TITLE: Controlling Nutritional Status (CONUT) Score as a Predictor of All-Cause Mortality at 3 Months in Stroke Patients

SHORT TITLE: Controlling Nutritional Status Score in Stroke

AUTHORS:

Fidel LÓPEZ-ESPUELA*

Bachelor Psychologist. Research Nurse

Email: fidel.lopez.es@gmail.com

Institution: University of Extremadura, Caceres, Spain

Raúl RONCERO-MARTÍN*, PhD, RN

Vice-Dean Nursing School

Email: rronmar@unex.es

Institution: Nursing Department, Nursing and Occupational Therapy College, University of Extremadura, Caceres, Spain

Juan Diego PEDRERA ZAMORANO, MD, PhD

Head of Nursing Department

Email: jpedrera@unex.es

Institution: University of Extremadura, Caceres, Spain

Purificación REY-SANCHEZ, PhD

Email: fidellopez@unex.es

Institution: Nursing Department, Nursing and Occupational Therapy College, University of Extremadura, Caceres, Spain

Ignacio ALIAGA-VERA, PhD

Email: i.aliaga@pdi.ucm.es

Institution: Nursing Department, Nursing and Occupational Therapy College, University of Extremadura, Caceres, Spain

Con formato: Inglés (Estados Unidos)

Con formato: Inglés (Estados Unidos)

Con formato: Inglés (Estados Unidos)

Con formato: Inglés (Estados Unidos)

Con formato: Italiano (Italia)

Con formato: Inglés (Estados Unidos)

Juan Carlos PORTILLA-CUENCA, MD

Neurologist

E-mail: portilla7819@yahoo.es

Institution: Stroke Unit, Hospital San Pedro de Alcantara, Caceres, Spain

Ignacio CASADO-NARANJO, MD

Head, Department of Neurology

Email: icasadon@gmail.com

Institution: Stroke Unit. Department of Neurology. Hospital San Pedro de Alcántara. Caceres. Spain.

José María MORÁN-GARCÍA, PhD

Email: jmmorang@unex.es

Institution: Nursing Department, Nursing and Occupational Therapy College, University of Extremadura, Caceres, Spain

Jesús María LAVADO-GARCÍA, PhD, RN

Dean, Nursing School

Email: jmlavado@unex.es

Institution: University of Extremadura, Caceres, Spain

CORRESPONDENCE:

Juan Diego PEDRERA ZAMORANO, MD, PhD

Head of Nursing Department

Email: jpedrera@unex.es

Phone: 0034927257456

Institution: University of Extremadura, Caceres, Spain

Con formato: Inglés (Estados Unidos)

Con formato: Español (España)

Con formato: Español (España)

Con formato: Español (España)

Con formato: Inglés (Estados Unidos)

Con formato: Inglés (Estados Unidos)

Con formato: Inglés (Estados Unidos)

Con formato: Inglés (Estados Unidos)

Con formato: Español (España)

Avda. de la Universidad S/N

CP, 10.003, Cáceres

FIGURES: 1 TABLES: 4

SOURCES OF FUNDING.

None.

ACKNOWLEDGMENTS

We appreciate the voluntary participation and collaboration ~~altruistic and disinterested~~ of all patients and their families.

To Irene, Jaime ~~y~~ and Elena.

DISCLOSURE STATEMENT

The authors report no conflicts of interest.

Con formato: Inglés (Estados Unidos)

Con formato: Inglés (Estados Unidos)

Con formato: Inglés (Estados Unidos)

Con formato: Inglés (Estados Unidos)

Con formato: Inglés (Estados Unidos)

Abstract

Malnutrition is frequently observed in patients after stroke and is associated with poor outcomes. Patients at risk of malnutrition may be identified with several nutrition screening tools, but ~~so far,~~ no nutritional screening tool has been validated for use with stroke patients. ~~We~~ The aim~~ed~~ of this study was to ~~demonstrate~~ explore the ~~cap~~ability of the Controlling Nutritional Status (CONUT) score to ~~anticipate~~ predict 3-month mortality in stroke patients. ***Methods:*** Patients were recruited from consecutive admissions at a hyperacute stroke unit and were screened for risk of malnutrition (light, moderate, ~~and~~ or severe) ~~according to their~~using CONUT scores. At the next visit, ~~Three~~3-month outcomes were obtained ~~from the following, consecutive visit for each patient~~. ***Results:*** Of the 164 recruited patients, 51.2% were male. ~~The m~~Mean patient age was 77.7 (SD = 7.0) years, and 85.8% of ~~the~~ patients had an ischemic stroke**.** ~~Regarding the classification of the patients by the CONUT score, t~~There was a ~~statistically~~ significant difference in the survival rate ($p < 0.001$) ~~and higher mortality~~ at ~~three~~ 3 months ~~among the~~between patients with moderate risk for malnourishment~~ed~~ compared to the other patients. The multivariate regression Cox model showed that modearate risk of ~~being~~ malnourishment~~ed~~, according to the CONUT score, increased the risk for death at 3 months (hazard ratio~~,~~ 1.086; 95% CI~~confidence interval~~, 1.057−8.305; $p < 0.039$). ***Conclusion:*** The CONUT score has predictive validity for ~~all~~ all-cause~~s of~~ mortality in stroke patients after 3~~three~~ months, both in hospital and after discharge. Further prospective multicenter studies with ~~multicenter and~~ larger samples are needed to clarify the usefulness of the CONUT score in the prognosis of ~~all~~ all-cause~~s of death~~ mortality in stroke patients.

Comentado [MW1]: Ok?

Comentado [F2R1]: Ok

KEYWORDS: Malnutrition; stroke; nutrition screening tool; mortality; Controlling Nutritional Status (CONUT) score

Stroke is one of the leading causes of mortality and disability worldwide as well as an enormous healthcare burden (Feigin et al., 2018; Feigin, Norrving, & Mensah, 2017). Malnutrition is frequently observed in stroke patients and is associated with poor outcomes, both in the acute and rehabilitation phases, including increased mortality and morbidity (Aliasghari et al., 2018; FOOD Trial Collaboration, 2003; Martineau, Bauer, Isenring, & Cohen, 2005; Zhang et al., 2015). Malnutrition at hospital admission predicts poor outcomes after stroke, and 1-week undernutrition was reported to predict poor 3-month outcomes (López-Espuela et al., 2017; Yoo et al., 2008;). ~~Thus, a~~As malnutrition is ~~often~~ an underrecognized and undertreated condition, previous authors have recommended the use of simple strategies to~~the early recognition~~ identify~~of those patients by simple strategies to identify~~ patients at risk of malnutrition ~~is recommended~~ during acute management (Sakai et al., 2019; Lieber et al., 2018; Lamb, Parr, Lamb, & Warren, 2009).

The guidelines for clinical nutrition in patients with stroke underline the importance of an early screening and assessment of dysphagia and the importance of providing advice to avoid malnutrition, highlighting the importance of patient screening for nutritional risk within the first days after hospital admission (Burgos et al., 2018; Wirth et al., 2013). However, there have been~~is a lack of~~, to this time, no validated screening and assessment tools for malnutrition in stroke patients (Rotilio et al., 2004). ~~Malnutrition, defined by the~~A number of instruments, including the Malnutrition Universal Screening Tool (MUST), Mini Nutritional Assessment-Short Form (MNA-SF), Subjective Global Assessment (SGA), Nutritional Risk Screening Tool-2002 (NRS-2002), Short Nutritional Assessment Questionnaire (SNAQ), Nutritional Risk Indicator (NRI), and Malnutrition Screening Tool (MST), have~~s~~ been used to predict~~associated with~~ adverse outcomes in hospitalized patients, but none of these

Con formato: Sangría: Primera línea: 1,25 cm

screening tools hasve been expressly validated in stroke patients (Gomes, Emery, & Weekes, 2016; Wirth et al., 2013). The Controlling Nutritional Status (CONUT) score is a malnutrition assessment tool that allows for early detection and follow up based on the evaluation of the serum albumin concentration, total peripheral lymphocyte count, and total cholesterol concentration (Ignacio de Ulíbarri et al., 2005). Naito et al. (2018) recently described Tthe CONUT score has been described recently as a useful prognostic marker of for 3-month functional outcomes in patients with acute ischemic stroke (Naito et al., 2018) and as for patient survival outcomes in among patients with variousdifferent conditions (Iwakami et al., 2017; Sun, Luo, Zhao, & Ye, 2017; Takagi et al., 2018; Yoshihisa et al., 2018). When stroke patients are hospitalized, the effects of nutritional status on their prognosis merit further evaluation. The applicability of scores such as CONUT in evaluating such patients has yet to be fully validated. The Our primary aimgoal of in the present study was to determine the ability of CONUT to independently predict mortality risk in acute stroke patients during the first 3 months post stroke.

Materials and Methods

Design

We performed an observational, prospective and, longitudinal study on among consecutive patients with a diagnosis of ischemic stroke or spontaneous, nontraumatic intracerebral hemorrhage who were admitted to our neurology unit (NU) at the Complejo Hospitalario Universitario in Cáceres (Spain).

Participants

From January through May 2016, 206 patients were admitted to the NU: oOf these 206 patients admitted to the NU from January through May 2016 patients, 16 declined to participate in the present study, 25 were could not commit to the follow-up

visit, and one ~~patient~~ was diagnosed with stroke mimic. Thus, a total of 164 patients were included ~~in this study~~. All of the participants provided written informed consent, and the Clinical Research Ethics Committee of ~~our~~ the ~~H~~hospital approved the research. We informed~~The~~ participants and family members ~~were told~~ that they could refuse to continue participation at any time and that refusal would not affect the quality of care in the institution~~,~~ and that their privacy would be respected and protected.

Measures

The same investigator collected participant ~~D~~data ~~were collected by one investigator~~ at two different times: within 48 hr after admission (to record the patients' ~~reported~~ baseline nutritional status) and ~~three~~ 3 months after the stroke. We collected the ~~The~~ following demographic variables ~~were registered~~: age~~;~~, gender~~;~~, comorbid conditions~~,~~ classified with the Charlson Comorbidity Index (CCI)~~;~~, stroke severity~~,~~ using the National Institutes of Health Stroke ~~s~~Scale (NIHSS)~~;~~, and presence of dysphagia. After ~~three~~ 3 months, we collected follow-up measures~~the situation was reassessed~~.

We measured ~~T~~the nutritional status of patients ~~was measured~~ with the Mini Nutritional Assessment (MNA™), a well-validated, 18-item tool used to assess nutritional status in older adults (Guigoz, 2006). ~~The i~~Items include a set of anthropometric measures (weight loss~~;~~, body mass index [BMI]~~;~~, and mid-arm and calf circumference in items B, F, Q, and R, respectively), a dietary questionnaire (number of meals consumed~~;~~, food and fluid intake~~;~~, and feeding autonomy within the past 24 hr in items J, K, L, M, and N, respectively), a global assessment (mobility~~;~~, presence of acute stress~~;~~, presence of dementia or depression~~;~~, lifestyle~~;~~, and medications in items C, D, E, G, and H, respectively), and a subjective assessment (self-perception of health and nutrition in ~~I~~items O and P, respectively). Lower MNA scores indicate poorer

Comentado [MW3]: You list 4 specific ítems but then provide 5 letters to go with the ítems. Is an ítem missing, or do 2 letters pertain to one of the ítems? It's just confusing because you use "respectively," which implies a one-to-one relationship.

Comentado [F4R3]: It´s ok, 2 letters correspong to 1 item.

nutrition~~ourishment;~~. S~~s~~cores range from 0 to 30, with scores of 17–23.5 indicating nutritional risk, and scores less than 17 indicating malnutrition.

We calculated ~~T~~the CONUT score (Ignacio de Ulíbarri et al., 2005) ~~was calculated~~ using levels of serum albumin, lymphocytes, and total cholesterol (range 0–12, higher = worse). In this scoring system, point values are assigned to different ranges of the laboratory measures as follows: serum albumin ≥ 3.5 g/dL~~,~~ = 0 points~~;~~, 3–3.49 ~~3~~ g/dL~~,~~ = 2 points~~;~~, 2.5–2.99 ~~2.5~~ g/dL~~,~~ = 4 points~~;~~, and < 2.5 g/dL~~,~~ = 6 points; lymphocytes ≥ 1600 cells/μL~~,~~ = 0 points~~;~~, 1200–1599 cells/μL~~,~~ = 1 point~~;~~, 800–1199 cells/μL~~,~~ = 2 points~~;~~, and < 800 cells/μL~~,~~ = 3 points; and total cholesterol ≥ 180 mg/dL~~,~~ = 0 points~~;~~, 140–179 mg/dL~~,~~ = 1 point~~;~~, 100–139 mg/dL~~,~~ = 2 points~~;~~, and < 100 mg/dL~~,~~ = 3 points. ~~Patients were also divided into three groups~~Patients are categorized as follows based on their CONUT score: light-CONUT (0–4), moderate-CONUT (5–8), and severe-CONUT (≥ 9). ~~In this~~ Because no patients received scores higher than 8 in the present study, we divided patients into two groups for our analyses based on their~~the~~ CONUT score~~s was categorized into two groups as follows~~: high CONUT group (CONUT score ≥ 5~~) (~~; malnutrition status) and low CONUT group (CONUT score 0–4~~) (~~; normal nutritional status~~) (~~; Honda et al., 2018; Shirakabe et al., 2018).

We documented ~~C~~comorbid conditions ~~were classified with~~using the CCI (Charlson, Pompei, Ales & MacKenzie, 1987) on the basis of the *International Classification of Diseases,* ~~Ninth~~9th ~~R~~revision, ~~C~~clinical ~~C~~codification codes. With the CCI, ~~E~~each comorbid condition is assigned a score of 1, 2, 3, or 6 depending on the risk of dying associated with ~~this condition~~it. Higher scores on the CCI indicate higher 10-year mortality risk.

Statistical Analysis

Comentado [MW5]: Edits ok?

Comentado [F6R5]: ok

Con formato: Fuente: Cursiva

Comentado [MW7]: Ok?

Comentado [F8R7]: It´s ok.

~~The~~ We analyzed data using SPSS, version 21.0 and express results ~~are expressed~~ as ~~the~~ means (standard deviations). To compare ~~B~~baseline characteristics between ~~each~~ groups ~~were compared~~ we used~~ing~~ the Chi square ~~test~~, Fisher exact ~~test~~, or Mann-Whitney U test as appropriate. We used ~~M~~multivariate Cox proportional hazards models ~~were performed~~ to determine the effects of independent variables on~~for the~~ outcomes. To analyze ~~T~~the impact of the CONUT score on all-cause mortality ~~was analyzed~~we used~~ing~~ Kaplan–Meier curves and log-rank tests. For the mortality analysis, the patients were censored at the time of death or at the last visit. We established ~~S~~statistical significance ~~was established~~ at ~~a value of~~ $p < 0.05$. ~~The data were analyzed using the SPSS statistical package version 21.0.~~

Comentado [MW9]: Ok?

Comentado [F10R9]: It´s ok.

Comentado [MW11]: I'm not sure what you mean by "censored" in this context. Can you explain?

Comentado [F12R11]: that the date of death was taken

Con formato: Fuente: Cursiva

Results

A total of 164 patients were included in the study, with a mean age of 77.7 (SD = 7.0) (, rang~~e from~~ = 65~~-~~ to 97) years. ~~Out of the patients~~Of these, 51.2% were men, 85.8% had an ischemic stroke, and 11.0% were diagnosed with dysphagia following the bedside screening test by nurses on admission to hospital. According to the CONUT score, ~~there were~~ we categorized 147 of the patients (89.6%) as~~at~~ light risk~~,~~ and 17 (10.4%) a~~t moderate risk, and none at~~ high risk of malnutrition. Using the MNA~~ini Nutritional Assessment~~ tool, we found that 106 patients (64.6%) ~~were considered~~had normal nutritional status, 51 (31.1%) were at risk of malnutrition ~~risk~~, and 7 (4.3%) were malnourished. We summarize the~~A~~ baseline description of the participants ~~is summarized~~ as a whole and by CONUT score risk group in Table 1.

Comentado [MW13]: Please carry out to the same decimal place that you carry out the mean, i.e., the tenth.

Comentado [F14R13]: 7.0

Con formato: Resaltar

Con formato: Resaltar

Comentado [MW15]: Ok? This was what you said you did for this study (i.e., two groups) and what you show in the table.

Comentado [F16R15]: Yes , Low and High

<Table 1 near here.>

~~Table 2 describes the main differences between stroke patients at baseline according to the CONUT score classification. No significant differences were~~We found no significant differences between the CONUT score risk groups ~~between the studied~~

~~groups in the~~for age, gender, type of stroke, ~~and~~ or CCI~~Charlson comorbidity index~~ (p > 0.05). ~~The l~~Length of hospital stay was ~~higher~~ longer and NIHSS score and percentage of patients with dysphagia were higher ~~in~~ for~~the~~ patients ~~with moderate malnutrition~~in the high CONUT risk group (p = 0.001, p = 0.008, and p = 0.025, respectively) ~~as well as the NIHSS score (p=0.008). The percentage of patients with dysphagia was also higher in the group with moderate malnutrition (p=0.025)~~.

At the ~~three~~ 3-month~~s of~~ follow up, mortality was 17.1% (n = 28). Of the 28 patients who ~~had~~ died, 8 (28.6%) ~~were~~ had been classified as moderately malnourished (and thus had been in our high group) according to the CONUT score, and their average age at the time of death was 81.2 (SD = 7.3~~)~~ ~~(~~, rang~~ing from~~ of 66 – ~~-~~94) years. As shown in Table 2~~3~~, mortality was significantly associated with ~~the~~ patient age, length of hospital stay and NIHSS score at baseline (p < 0.01). We found ~~N~~no significant differences ~~were found~~ in gender ~~and~~ or type of stroke between ~~the groups~~survivors and nonsurvivors (p > 0.05). ~~The occurrence of d~~Dysphagia, comorbidity and moderate malnutrition w~~as~~ere all significantly higher in the ~~patients who had died~~nonsurvivors (p < 0.01).

<Table 2~~3~~ near here.>

We analyzed ~~T~~the time to mortality ~~was analyzed~~ by Kaplan-Meier survival curves based on the CONUT score. Patients with light malnutrition had a minor risk of mortality compared to patients with moderate malnutrition (p < 0.001~~)~~ ~~(~~; Figure 1). Table ~~4~~ summarizes our ~~A~~analysis ~~by proportional hazard model is summarized in Table 4, which presents~~of the associations of the CONUT score with mortality at ~~three~~ 3 months after stroke by proportional hazard model. We found that ~~M~~moderate malnutrition according to the CONUT score was associated with an increased risk of

Con formato: Fuente: Cursiva

Comentado [F17]: Table 2

Con formato: Tachado

Comentado [F18]: Table 2

Con formato: Tachado

Con formato: Tachado

Comentado [F19]: Table 3

~~three~~3-month mortality in stroke patients (~~H~~hazard ~~R~~ratio 1.086, 95% CI 1.057–~~-~~8.305, *p* = 0.039).

<Figure 1 and Table ~~4~~3 near here.>

Comentado [F20]: Table 3

Discussion

In the management of stroke patients, clinicians often lack knowledge concerning nutritional support, leading to a lack of consideration of the patient's nutritional status (Zheng et al., 2015). The American Stroke Association and American Heart Association guidelines for the early management of patients with acute ischemic stroke recommend that all ~~stroke patients~~ should be evaluated for their baseline nutritional status and that any malnutrition should be corrected or improved as soon as possible (Powers et al., 2018). In ~~this~~ the present study, we proposed, for the first time, using the nutrition screening tool CONUT as an indicator of the risk of mortality at ~~three~~ 3 months in stroke patients after adjusting for clinically relevant covariates.

The unfavorable prognostic impact of poor nutritional status in diseased individuals has been widely described, so ~~the application of~~ nutrition screening tools ~~is~~ are ~~becoming~~ useful for nurses and other health professionals ~~to~~ for the assessment patient prognosis. Several nutrition screening tools have been used in stroke patients, such as the MNA, ~~(~~conducted mainly by questionnaire in combination with BMI ~~body mass index~~ (~~BMI;~~ Aliasghari et al., 2018; Hsieh et al., 2017; Zhao et al., 2017); the Geriatric Nutritional Risk Index (GNRI), a simple and well-established nutritional~~l~~ screening tool that predicts poor prognosis in elderly patients and in those with a high risk of cardiovascular events (Maruyama, Nakagawa, Koyama, Maruyama, & Hasebe, 2018); the malnutrition assessment according to the definition of malnutrition from the European Society of Clinical Nutrition and Metabolism (ESPEN; Burgos et al., 2018; Marco et al., 2018); and the Malnutrition Universal Screening Tool (MUST;

Comentado [MW21]: For consistency throughout the manuscript.

Comentado [F22R21]: Perfect

Dworzynski, Ritchie, & Playford, 2015; Hookway, Gomes, & Weekes, 2015; Sabbouh & Torbey, 2017). Other nutrition screening tools have also been developed, such as the Nutritional Risk Screening 2002 (NRS 2002) ~~or~~ and the Subjective Global Assessment (Kondrup, Allison, Elia, Vellas, & Plauth, 2003; Sabbouh & Torbey, 2017). The Controlling Nutritional Status (CONUT) score was initially proposed and validated as a nutrition screening tool for hospitalized patients (Ignacio de Ulíbarri et al., 2005) and further used in patients with acute heart failure (Iwakami et al., 2017) or cancer (Iseki et al., 2015; Toyokawa et al., 2016). Recently, researchers showed ~~the use of~~ the CONUT score ~~has been shown~~ to be a useful prognostic marker of ~~three~~3-month functional outcomes in patients with acute ischemic stroke (Naito et al., 2018); however, to our knowledge, there ~~are~~ have been no data, to this point, about the usefulness of the CONUT score to predict a negative prognosis in patients with stroke.

Comentado [MW23]: Are these tools that have not been used in stroke patients?

Comentado [F24R23]: These are tools that have once been used in stroke patients.

Malnutrition is prevalent in stroke patients, and ~~its~~ early recognition significantly ~~affects the~~improves outcomes in these patients (Sabbouh & Torbey, 2017). Malnutrition on admission to the hospital after acute stroke is associated with poor 1-~~month~~ and 3-month outcomes, including increased length of stay and increased prevalence of dysphagia and complications (Dávalos et al., 1996; Davis et al., 2004; Gariballa, Parker, Taub, & Castleden, 1998; Kokura, Maeda, Wakabayashi, Nishioka, & Higashi, 2016; Martineau et al., 2005; Maruyama et al., 2018; Yoo et al., 2008). Due to the lack of validated nutrition screening tools for stroke patients, authors report ~~there is~~ a wide range of malnutrition ~~reported~~ in stroke patients across the literature (from 6.1% to 62%; Foley, Salter, Robertson, Teasell, & Woodbury, 2009). ~~Based on~~Using the CONUT score, we found that 10.4% of the patients in the present study had a moderate risk for malnutrition, which is within the ranges reported in the literature. We did not observe cases of actual malnutrition within the studied sample, but our results indicate

Comentado [MW25]: Ok?

Comentado [F26R25]: ok

that, even at a moderate risk of malnutrition, the incidence of all-cause mortality might be increased in stroke patients. Previous researchers have proposed ~~B~~being at risk of malnutrition ~~has been proposed~~ as a significant and independent predictor of mortality at 6 months (Gomes et al., 2016), 3 and 6 months (Stratton, King, Stroud, Jackson, & Elia, 2006) and 3 years (Lim et al., 2012) post stroke~~.~~. ~~with r~~Routine screening of stroke patients for risk of malnutrition is thus recommended.

The independent association between CONUT score at hospital admission and 3-month mortality is not a novel finding, but the large confidence interval for HRs associated with the CONUT score (HR 1.086, 95% CI 1.057–~~–~~8.305, p = 0.039) suggests that larger samples are required to adequately investigate the clinical relationship between malnutrition assessed with the CONUT score and mortality following acute stroke.

Comentado [MW27]: Is this what you mean? If not, what variable are you referring to with "hospital admission"?

Comentado [F28R27]: Upon admission of patients to the hospital

Although the main aim of ~~our~~ the present study was to evaluate the predictive value of the CONUT score ~~on~~ for 3-month mortality, other nutrition~~al~~ screening tools are also important, as a standard of malnutrition assessment for stroke patients is lacking, with different scoring systems yielding different ratings. Although nutritional care is a multidisciplinary activity, nurses have~~the~~ a fundamental ~~contribution of nursing has been recognized~~role to play, ~~including the~~which require~~sment for~~ sufficient numbers of nutritionally aware and skilled nurses to fulfill (Kayser-Jones & Schell, 1997; Kowanko, 1997; Perry, Hamilton, Williams, & Jones, 2013). Nurses are in a prime position to identify malnutrition and perform a crucial role in its prevention and management (Mold, 2010).

The prospective, consecutive nature of ~~our~~ the present study provides a robust audit of clinical practice in association with inpatients with acute stroke ~~inpatients~~ and is inclusive of a 3-month mortality follow up. The identification of malnutrition measured

with the CONUT score as an independent predictor of 3-month mortality highlights the need for ~~consideration of~~updated intervention guidelines~~,~~ and audit datasets and future research to further explore the associations between nutrition and survival outcomes in stroke patients.

We also recognize several limitations in ~~our~~ the present study. The CONUT score works as a screening tool for malnutrition rather than a specific measure of nutritional status, which could limit its utility for planning patient care. ~~We have a relatively~~Our ~~small~~ sample size was relatively small and the follow-up period relatively short ~~follow~~. Further, all participants were from ~~up in~~ a single acute unit~~, and~~; thus our analysis may suffer some selection bias. The results of the multivariable Cox proportional hazards model presented in Table 3 ~~5~~ 4 ~~may~~ also suggest that the convenience sample may have been inadequately powered to demonstrate statistical significance for some of the studied covariates (age, dysphagia, type of stroke). There is no universally accepted definition of malnutrition or a gold standard for the assessment of nutritional status. We also lack information about detailed dietary intake ~~at~~ during hospitalization as well as other body composition parameters, such as body fat or lean mass, of the patients.

In conclusion, this is the first study to show that the CONUT score has predictive validity for ~~all~~ all-cause~~s of~~ mortality ~~in~~ 3 months after stroke ~~patients after three months~~, both in hospital and after discharge. Further prospective studies with multicenter and larger samples are needed to clarify the usefulness of the CONUT score in the prognosis of all causes of death in stroke patients. Strategies to identify and treat malnutrition should be routinely considered in existing clinical audits, intervention guidelines and future research in stroke patients.

Comentado [MW29]: Edits ok?

Comentado [F30R29]: ok

Comentado [MW31]: Correct?

Comentado [F32R31]: Now, it is table 3

Con formato: Resaltar

Figure Caption

Figure 1. Kaplan-Meier diagram reflecting the cumulative proportion of surviving patients according to the CONUT score categories: low (< 4) or high (≥ 5).

CONUT = Controlling Nutritional Status. ~~P~~ *p* < 0.001 by log rank test.

Comentado [MW33]: The graph goes out well beyond the 3 months of the present study. Is that ok?

Comentado [F34R33]: Ok,

References

Aliasghari, F., Izadi, A., Khalili, M., Farhoudi, M., Ahmadiyan, S., & Deljavan, R. (2018). Impact of premorbid malnutrition and dysphagia on ischemic stroke outcome in elderly patients: A community-based study. *Journal of the American College of Nutrition*, 1-9. doi:10.1080/07315724.2018.1510348

Burgos, R., Bretón, I., Cereda, E., Desport, J. C., Dziewas, R., Genton, L., . . . Bischoff, S. C. (2018). ESPEN guideline clinical nutrition in neurology. *Clinical Nutrition (Edinburgh, Scotland), 37*(1), 354-396. doi:10.1016/j.clnu.2017.09.003

Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbility in longitudinal studies: Development and validation. J Chronic Dis 1987;40:373-83.

Dávalos, A., Ricart, W., Gonzalez-Huix, F., Soler, S., Marrugat, J., Molins, A., . . . Genís, D. (1996). Effect of malnutrition after acute stroke on clinical outcome. *Stroke, 27*(6), 1028-1032.

Davis, J. P., Wong, A. A., Schluter, P. J., Henderson, R. D., O'Sullivan, J. D., & Read, S. J. (2004). Impact of premorbid undernutrition on outcome in stroke patients. *Stroke, 35*(8), 1930-1934. doi:10.1161/01.STR.0000135227.10451.c9

Dworzynski, K., Ritchie, G., & Playford, E. D. (2015). Stroke rehabilitation: Long-term rehabilitation after stroke. *Clinical Medicine (London, England), 15*(5), 461-464. doi:10.7861/clinmedicine.15-5-461

Feigin, V. L., Nguyen, G., Cercy, K., Johnson, C. O., Alam, T., Parmar, P. G., et al. (2018). Global, Regional, and Country-Specific Lifetime Risks of Stroke, 1990 and 2016. *The New England journal of medicine,* 379(25),2429-2437. doi: 10.1056/NEJMoa1804492

Comentado [MW35]: Please note that, in the interest of time, I do not edit the Reference List or the in-text citations. Please take one more look at these before we submit the manuscript to Sage for publication.

Comentado [F36R35]: Ok,

Con formato: Inglés (Estados Unidos)

Con formato: Inglés (Estados Unidos)

Con formato: Italiano (Italia)

Feigin, V. L., Norrving, B., Mensah, G. A. (2017). Global Burden of Stroke. *Circulation Research*, 120,439-448. doi: 10.1161/CIRCRESAHA.116.308413.

Foley, N. C., Salter, K. L., Robertson, J., Teasell, R. W., & Woodbury, M. G. (2009). Which reported estimate of the prevalence of malnutrition after stroke is valid? *Stroke, 40*(3), 66. doi:10.1161/STROKEAHA.108.518910

FOOD Trial Collaboration. (2003). Poor nutritional status on admission predicts poor outcomes after stroke: observational data from the FOOD trial. *Stroke, 34*(6), 1450-1456

Gariballa, S. E., Parker, S. G., Taub, N., & Castleden, C. M. (1998). Influence of nutritional status on clinical outcome after acute stroke. *The American Journal of Clinical Nutrition, 68*(2), 275-281. doi:10.1093/ajcn/68.2.275

Gomes, F., Emery, P. W., & Weekes, C. E. (2016). Risk of malnutrition is an independent predictor of mortality, length of hospital stay, and hospitalization costs in stroke patients. *Journal of Stroke and Cerebrovascular Diseases: The Official Journal of National Stroke Association, 25*(4), 799-806. doi:10.1016/j.jstrokecerebrovasdis.2015.12.017

Guigoz, Y. (2006). The Mini Nutritional Assessment (MNA) review of the literature—What does it tell us? *Journal of Nutrition, Health, an Aging,* 10, 466–485.

Honda, Y., Yamawaki, M., Shigemitsu, S., Kenji, M., Tokuda, T., Tsutumi M, . . . Ito, Y. (2018) Prognostic value of objective nutritional status after transcatheter aortic valve replacement. *Journal of cardiology,* pii: S0914-5087(18)30341-1. doi: 10.1016/j.jjcc.2018.11.013.

Hookway, C., Gomes, F., & Weekes, C. E. (2015). Royal college of physicians intercollegiate stroke working party evidence-based guidelines for the secondary prevention of stroke through nutritional or dietary modification. *Journal of*

Con formato: Inglés (Estados Unidos)

Human Nutrition and Dietetics: The Official Journal of the British Dietetic Association, 28(2), 107-125. doi:10.1111/jhn.12248

Hsieh, D., Hung, J., Chang, K., Huang, Y., Lee, T., & Chen, H. (2017). Malnutrition in acute stroke patients stratified by stroke severity- A hospital based study. *Acta Neurologica Taiwanica, 26(3)*, 120-127. Retrieved from https://www.ncbi.nlm.nih.gov/

Ignacio de Ulíbarri, J., González-Madroño, A., de Villar, N. G. P., González, P., González, B., Mancha, A., . Fernández, G. (2005). CONUT: A tool for controlling nutritional status. first validation in a hospital population. *Nutricion Hospitalaria, 20*(1), 38-45.

Iseki, Y., Shibutani, M., Maeda, K., Nagahara, H., Ohtani, H., Sugano, K., . . . Hirakawa, K. (2015). Impact of the preoperative controlling nutritional status (CONUT) score on the survival after curative surgery for colorectal cancer. *PloS One, 10*(7), e0132488. doi:10.1371/journal.pone.0132488

Iwakami, N., Nagai, T., Furukawa, T. A., Sugano, Y., Honda, S., Okada, A., . . . Anzai, T. (2017). Prognostic value of malnutrition assessed by controlling nutritional status score for long-term mortality in patients with acute heart failure. *International Journal of Cardiology, 230*, 529-536. doi:10.1016/j.ijcard.2016.12.064

Kayser-Jones, J., & Schell, E. (1997). The effect of staffing on the quality of care at mealtime. *Nursing Outlook, 45*(2), 64-72.

Kokura, Y., Maeda, K., Wakabayashi, H., Nishioka, S., & Higashi, S. (2016). High nutritional-related risk on admission predicts less improvement of functional independence measure in geriatric stroke patients: A retrospective cohort study. *Journal of Stroke and Cerebrovascular Diseases: The Official Journal of*

Con formato: Inglés (Estados Unidos)

National Stroke Association, 25(6), 1335-1341. doi:10.1016/j.jstrokecerebrovasdis.2016.01.048

Kondrup, J., Allison, S. P., Elia, M., Vellas, B., & Plauth, M. (2003). ESPEN guidelines for nutrition screening 2002. *Clinical Nutrition (Edinburgh, Scotland), 22*(4), 415-421.

Kowanko, I. (1997). The role of the nurse in food service: A literature review and recommendations. *International Journal of Nursing Practice, 3*(2), 73-78.

Lamb, C. A., Parr, J., Lamb, E. I. M., & Warren, M. D. (2009). Adult malnutrition screening, prevalence and management in a united kingdom hospital: Cross-sectional study. *The British Journal of Nutrition, 102*(4), 571-575. doi:10.1017/S0007114509236038

Lieber, A.C., Hong, E., Putrino, D., Nistal, D.A., Pan, J.S., Kellner, C.P. (2018). Nutrition, Energy Expenditure, Dysphagia, and Self-Efficacy in Stroke Rehabilitation: A Review of the Literature. *Brain Sciences,* 8(12). pii: E218. doi: 10.3390/brainsci8120218.

Lim, S. L., Ong, K. C. B., Chan, Y. H., Loke, W. C., Ferguson, M., & Daniels, L. (2012). Malnutrition and its impact on cost of hospitalization, length of stay, readmission and 3-year mortality. *Clinical Nutrition (Edinburgh, Scotland), 31*(3), 345-350. doi:10.1016/j.clnu.2011.11.001

López Espuela, F., Portilla Cuenca, J.C., Holguín Mohedas, M., Párraga Sánchez, J.M., Cordovilla-Guardia, S., Casado Naranjo, I. (2017). [Nutritional status and the relationship regarding functional status after stroke]. *Nutricion Hospitalaria,* 34(5),1353-1360. doi: 10.20960/nh.874.

Marco, E., Sánchez-Rodríguez, D., Dávalos-Yerovi, V. N., Duran, X., Pascual, E. M., Muniesa, J. M., . . . Duarte, E. (2018). Malnutrition according to ESPEN

Con formato: Inglés (Estados Unidos)

Con formato: Inglés (Estados Unidos)

consensus predicts hospitalizations and long-term mortality in rehabilitation patients with stable chronic obstructive pulmonary disease. *Clinical Nutrition (Edinburgh, Scotland),* doi:10.1016/j.clnu.2018.09.014

Martineau, J., Bauer, J. D., Isenring, E., & Cohen, S. (2005). Malnutrition determined by the patient-generated subjective global assessment is associated with poor outcomes in acute stroke patients. *Clinical Nutrition (Edinburgh, Scotland), 24*(6), 1073-1077. doi:10.1016/j.clnu.2005.08.010

Maruyama, K., Nakagawa, N., Koyama, S., Maruyama, J., & Hasebe, N. (2018). Malnutrition increases the incidence of death, cardiovascular events, and infections in patients with stroke after rehabilitation. *Journal of Stroke and Cerebrovascular Diseases: The Official Journal of National Stroke Association, 27*(3), 716-723. doi:10.1016/j.jstrokecerebrovasdis.2017.10.002

Mould, J. (2010). Nurses 'must' control of the nutritional needs of stroke patients. *British Journal of Nursing (Mark Allen Publishing), 18*(22), 1410-1414. doi:10.12968/bjon.2009.18.22.45572

Naito, H., Nezu, T., Hosomi, N., Aoki, S., Kinoshita, N., Kuga, J., . . . Maruyama, H. (2018). Controlling nutritional status score for predicting 3-mo functional outcome in acute ischemic stroke. *Nutrition (Burbank, Los Angeles County, Calif.), 55-56*, 1-6. doi:10.1016/j.nut.2018.02.025

Perry, L., Hamilton, S., Williams, J., & Jones, S. (2013). Nursing interventions for improving nutritional status and outcomes of stroke patients: Descriptive reviews of processes and outcomes. *Worldviews on Evidence-Based Nursing, 10*(1), 17-40. doi:10.1111/j.1741-6787.2012.00255.x

Powers, W. J., Rabinstein, A. A., Ackerson, T., Adeoye, O. M., Bambakidis, N. C., Becker, K., . . . Tirschwell, D. L. (2018). 2018 guidelines for the early

management of patients with acute ischemic stroke: A guideline for healthcare professionals from the american heart association/american stroke association. *Stroke, 49*(3), e110. doi:10.1161/STR.0000000000000158

Rotilio, G., Canani, R. B., Branca, F., Cairella, G., Fieschi, C., Garbagnati, F., . . . Scalfi, L. (2004). Nutritional recommendations for the management of stroke patients. *Rivista Italiana Di Nutrizione Parenterale Ed Enterale, 22*(4), 227-236. Retrieved from https://moh-it.pure.elsevier.com/en/publications/nutritional-recommendations-for-the-management-of-stroke-patients

Sabbouh, T., & Torbey, M. T. (2017). Malnutrition in stroke patients: Risk factors, assessment, and management. *Neurocritical Care,* doi:10.1007/s12028-017-0436-1

Sakai, K., Kinoshita, S., Tsuboi, M., Fukui, R., Momosaki, R., Wakabayashi, H. (2019). Effects of Nutrition Therapy in Older Stroke Patients Undergoing Rehabilitation: A Systematic Review and Meta-Analysis. *The journal of nutrition, health & aging,* 23(1), 21-26. doi: 10.1007/s12603-018-1095-4.

Shirakabe, A., Hata, N., Kobayashi, N., Okazaki, H., Matsushita, M., Shibata, Y., et al. (2018). The prognostic impact of malnutrition in patients with severely decompensated acute heart failure, as assessed using the Prognostic Nutritional Index (PNI) and Controlling Nutritional Status (CONUT) score. *Heart and vessels,* 33, 134-44.

Stratton, R. J., King, C. L., Stroud, M. A., Jackson, A. A., & Elia, M. (2006). 'Malnutrition universal screening tool' predicts mortality and length of hospital stay in acutely ill elderly. *The British Journal of Nutrition, 95*(2), 325-330.

Sun, X., Luo, L., Zhao, X., & Ye, P. (2017). Controlling nutritional status (CONUT) score as a predictor of all-cause mortality in elderly hypertensive patients: A

Con formato: Italiano (Italia)

Con formato: Italiano (Italia)

prospective follow-up study. *BMJ Open, 7*(9), e015649. doi:10.1136/bmjopen-2016-015649

Takagi, K., Umeda, Y., Yoshida, R., Nobuoka, D., Kuise, T., Fushimi, T., . . . Yagi, T. (2018). Preoperative controlling nutritional status score predicts mortality after hepatectomy for hepatocellular carcinoma. *Digestive Surgery,* doi:10.1159/000488215

Toyokawa, T., Kubo, N., Tamura, T., Sakurai, K., Amano, R., Tanaka, H., . . . Ohira, M. (2016). The pretreatment controlling nutritional status (CONUT) score is an independent prognostic factor in patients with resectable thoracic esophageal squamous cell carcinoma: Results from a retrospective study. *BMC Cancer, 16*, 722. doi:10.1186/s12885-016-2696-0

Wirth, R., Smoliner, C., Jäger, M., Warnecke, T., Leischker, A. H., & Dziewas, R. (2013). Guideline clinical nutrition in patients with stroke. *Experimental & Translational Stroke Medicine, 5*(1), 14. doi:10.1186/2040-7378-5-14

Yoo, S., Kim, J. S., Kwon, S. U., Yun, S., Koh, J., & Kang, D. (2008). Undernutrition as a predictor of poor clinical outcomes in acute ischemic stroke patients. *Archives of Neurology, 65*(1), 39-43. doi:10.1001/archneurol.2007.12

Yoshihisa, A., Kanno, Y., Watanabe, S., Yokokawa, T., Abe, S., Miyata, M., . . . Takeishi, Y. (2018). Impact of nutritional indices on mortality in patients with heart failure. *Open Heart, 5*(1), e000730. doi:10.1136/openhrt-2017-000730

Zhang, J., Zhao, X., Wang, A., Zhou, Y., Yang, B., Wei, N., et al. (2015). Emerging malnutrition during hospitalization independently predicts poor 3-month outcomes after acute stroke: data from a Chinese cohort. *Asia Pacific journal of clinical nutrition,*24(3),379-86. doi: 10.6133/apjcn.2015.24.3.13.

Con formato: Italiano (Italia)

Zhao, N. -., Zeng, K. -., Wang, Y. -., Sheng, P. -., Tang, C. -., Xiao, P., & Liu, X. -. (2017). Research on the nutrition and cognition of high-risk stroke groups in community and the relevant factors. *European Review for Medical and Pharmacological Sciences, 21*(23), 5408-5414. doi:10.26355/eurrev_201712_13928

Zheng, T., Zhu, X., Liang, H., Huang, H., Yang, J., & Wang, S. (2015). Impact of early enteral nutrition on short term prognosis after acute stroke. *Journal of Clinical Neuroscience: Official Journal of the Neurosurgical Society of Australasia, 22*(9), 1473-1476. doi:10.1016/j.jocn.2015.03.028

Table 1. Baseline clinical characteristics of patients with acute stroke by CONUT Score Risk Group.

Characteristic	Total Patients *N* = 164	Low CONUT Risk Score *n* = 147	High CONUT Risk Score *n* = 17	*p*-value
Age (years), mean (SD)	77.7 (7.0)	77.6 (7.0)	78.0 (7.3)	0.863
Gender (male), *n* (%)	84 (51.2)	73 (49.7)	11 (64.7)	0.24[a]
Length of hospital stay (days), mean (SD)/range	9.0 (6.0)/2−42	8.0 (6.0)	14.0 (8.0)	0.001***
Type of stroke, *n* (%)				0.268[b]
Ischemic	139 (85.8)	126 (86.9)	13 (76.5)	
Hemorrhagic	23 (14.2)	19 (13.1)	4 (23.5)	
NIHSS score, mean (SD)/range	7.1 (6.8)/0−27	6.5 (6.3%)	12.0 (8.6)	0.008**
Dysphagia	18 (11.0)	13 (8.9)	5 (29.4)	0.025*[b]
Charlson Comorbidity Index				0.486[a]
None	66 (40.5)	60 (41.1)	6 (35.3)	
Moderate	47 (28.8)	40 (27.4)	7 (41.2)	
High	50 (30.7)	46 (31.5)	4 (23.5)	
Mini Nutritional Assessment				
Normal	106 (64.6)			
At risk for malnutrition	51 (31.1)			
Malnourished	7 (4.3)			

Note. CONUT = Controlling Nutritional Status; NIHSS = National Institutes of Health Stroke Scale.
[a]Chi square test.
[b]Fisher's exact test.
*Significant at $p < 0.05$.
**Significant at $p < 0.01$
***Significant at $p < 0.001$.

Comentado [MW37]: I combined Tables 1 and 2. Ok?

Comentado [F38R37]: OK

Comentado [MW39]: The number of patients accounted for in Type of Stroke only adds up to 162. Were there missing data on 2 or is this an error?

Comentado [F40R39]: Missing data on 2.

Comentado [MW41]: You did not list these data in Table 2 by CONUT score group. Do you want to add that? If not, we could just report this in the text and remove from table. Would that work for you?

Comentado [F42R41]: Add in Table 2 , ok

Table 2 Demographic, clinical and prognostic parameters in the univariate analysis of participating patients by 3-month survival outcome.

Parameter	Survivor	Nonsurvivor	*p*-value
Age (years), mean (SD)	77.0 (6.8)	81.2 (7.3)	0.003**
Gender (male), *n* (%)	71 (52.2)	13 (46.4)	0.587[a]
Length of hospital stay (days), mean (SD)	8.0 (5.0)	14.0 (8.0)	< 0.001***
Type of stroke, *n* (%)			0.372[b]
Ischemic	114 (84.4)	25 (92.6)	
Hemorrhagic	21 (15.6)	2 (7.4)	
NIHSS baseline score, mean (SD)	6.0 (5.7)	13.0 (8.7)	< 0.001***
Dysphagia, *n* (%)	11 (8.1)	7 (25.9%)	0.007[a]**
Charlson Comorbidity Index, *n* (%)			0.005[a]**
None	61 (44.9)	5 (18.5)	
Moderate	40 (29.4)	7 (25.9)	
High	35 (25.7)	15 (55.6)	
CONUT baseline score, *n* (%)			0.001[a]***
Low	127 (93.4)	20 (71.4)	
High	9 (6.6)	8 (28.6)	

Note. CONUT = Controlling Nutritional Status; NIHSS = National Institutes of Health Stroke Scale.
[a]Chi square test.
[b]Fisher's exact test.
Significant at $^{**}p < 0.01$; $^{***}p < 0.001$

Comentado [F43]: This table is ok

Comentado [F44R43]: Ok, but is table 2

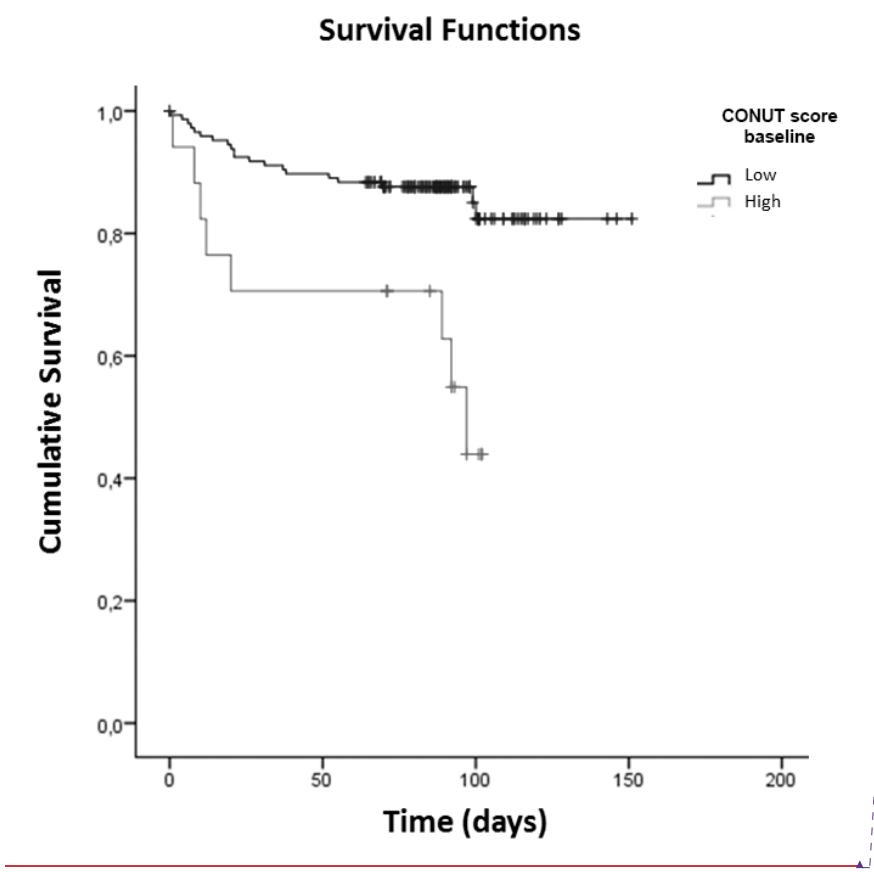
Table 3: Multivariable Cox proportional hazards model showing the effect of different variables on 3-month mortality among participating stroke patients (*N* = 164).

Variable	Beta (95% CI)	*p*-value
Age	0.043 (0.982-1.110)	0.165
Gender	0.042 (0.455-2.391)	0.921
Type of stroke	-0.489 (0.136-2.758)	0.524
NIHSS score baseline	0.091 (1.031-1.164)	0.003**
Dysphagia	-0.180 (0.275-2.536)	0.750
Charlson Comorbidity Index	0.362 (1.048-1.967)	0.024*
CONUT score	1.086 (1.057-8.305)	0.039*

Note. CONUT = Controlling Nutritional Status; NIHSS = National Institutes of Health Stroke Scale.

Significant at $^{*}p < 0.05$; $^{**}p < 0.01$.

Comentado [F45]: Ok, it´s table 3



Con formato: Inglés (Estados Unidos)