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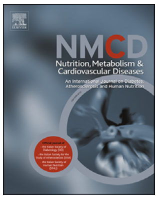

SYSTEMATIC REVIEWS AND META-ANALYSES

Controlling Nutritional Status (CONUT) score and the risk of mortality or impaired physical function in stroke patients: A systematic review and meta-analysis

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Abstract *Aims:* The Controlling Nutritional Status (CONUT) score is a tool for assessing the risk of malnutrition (undernutrition) that can be calculated from albumin concentration, total peripheral lymphocyte count, and total cholesterol concentration. CONUT score has been proposed as a promising prognostic marker in several clinical settings; however, a consensus on its prognostic value in patients with stroke is lacking. The aim of this systematic review and meta-analysis was to evaluate the relationship between CONUT score and clinical outcomes in patients with stroke based on all current available studies.

Data synthesis: Systematic research on PubMed, Scopus and Web of Science from inception to February 2023 was performed on the association between CONUT score and clinical outcomes in patients with stroke. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses were followed. Methodological quality was evaluated using the Newcastle-Ottawa Scale quality assessment tool. Pooled effect estimation was calculated by a random-effect model.

Through the initial literature search, 15 studies (all high-quality) including 16 929 patients were found to be eligible and analysed in the meta-analysis.

A significant risk of malnutrition (in most studies defined by a CONUT score $\geq$5) was directly associated with mortality, higher risk of poor functional outcome according to the modified Rankin Scale and total infection development. Evidence was consistent for acute ischaemic stroke and preliminary for acute haemorrhagic stroke.

Conclusion: CONUT score is an independent prognostic indicator, and it is associated with major disability and infection development during hospitalisation.

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1. Introduction

Stroke is a common disease worldwide in older people, with thrombotic or embolic occlusion of a cerebral artery more prevalent than intracerebral haemorrhage; it is a primary cause of mortality and also produces major disability, leading to loss of independence, the need for long term care either at home or in a nursing home and a high overall burden on healthcare [1]. Malnutrition (undernutrition) after stroke may be due to the interaction of several factors, including age itself and comorbidities, inflammation, dysphagia, hemiparesis, low nutrient intake, decreased mobility, depression and post-stroke dementia [1]. From a clinical point of view, a strong association has been found in the short and long term between poor nutritional status and adverse outcomes such as infection, increased prevalence of complications, longer hospital stay, reduced activities of daily living, hospitalisation costs and mortality [1,2].

The prevalence of malnutrition in patients with stroke, which is largely under-recognised [3], has however been estimated to be 6.1–62.0% in a systematic review based on 18 studies [4]. In the case of stroke, a wide variability in the prevalence of malnutrition has been observed, which may be explained by differences in diagnostic approach, time point of assessment and type of patients considered [4,5]. Specifically, various approaches/tools have been used for nutritional screening, nutritional assessment and nutrition diagnosis [1,4,5], for instance, the Geriatric Nutritional Risk Index (GNRI), the Prognostic Nutritional Index (PNI), the Subjective Global Assessment, the Mini Nutritional Assessment (MNA), etc. [1,5]. From a practical point of view, some approaches/tools cannot easily be applied in patients with stroke (especially in the acute phase) because of the difficulties in gathering proper information, for instance, those on body composition and/or recent weight loss. Thus, not surprisingly, much interest has been focused on the Controlling Nutritional Status (CONUT) score that is a tool requiring simple information on a few haemato-biochemical tests, which can also be applied in retrospective studies.

CONUT score was proposed as a screening tool of the risk of malnutrition in in-hospital patients and can be calculated from serum/plasma albumin concentration, total peripheral lymphocyte count and total serum/plasma cholesterol concentration (easily measured from a venous blood sample), which are proxy markers of protein metabolism, impaired immune defences and energy deficiency, respectively; the risk of malnutrition is classified as normal (score 0–1), light (2–4), moderate (5–8) and severe (9–12) [6]. In the last few years, several papers have proposed CONUT score as a promising prognostic marker in the clinical setting, for instance, in patients with cancer [7], coronary artery disease [8] or acute heart failure [9]; on the other hand, despite a reasonable number of papers [2,10–22], a consensus on the prognostic value of CONUT score in patients with stroke is lacking.

Facing this scenario and due to the number of recent studies published in the literature, the aim of the present systematic review and meta-analysis was to evaluate the relationships between CONUT score and clinical outcomes (mortality, disability and infection development) in patients with stroke based on all current available studies, with an additional analysis separately for acute ischaemic (AIS) and acute haemorrhagic (AHS) stroke.

2. Methods

2.1. Data sources and search strategy

Two authors (ODV and LS) independently performed a systematic literature search until 21 February 2023 of PubMed, Scopus and Web of Science. The following terms were used as a search strategy string on full texts in each database: (CONUT OR “Controlling Nutritional Status”) AND (stroke OR cerebrovascular); (CONUT OR “Controlling Nutritional Status”) AND (stroke OR cerebrovascular) AND mortality; (CONUT OR “Controlling Nutritional Status”) AND (stroke OR cerebrovascular) AND (disability OR outcome*); CONUT OR (CONUT OR “Controlling Nutritional Status”) AND (stroke OR cerebrovascular) AND infection*. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [23] were followed for performing the present review. The search was limited to reports in the English language without any limitations regarding the year of publication. Due to the study type (systematic review), ethical approval was not required. The study protocol was preregistered in the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42022324318).

Eligibility criteria were a) studies on patients with AIS and/or AHS stroke; b) studies reporting the prevalence of the risk of malnutrition according to CONUT score; c) studies reporting the cut-off value for high CONUT score; d) studies reporting the relationship between CONUT score and outcomes of interest after stroke (mortality, disability and infections); e) full papers published in peer-reviewed journals. Articles without full-text availability, opinion pieces, conference abstracts, review articles, case reports and editorials were excluded.

2.2. Study selection and data extraction

Titles and abstracts from the electronic searches were screened independently by two authors (ODV and LS). The full texts of selected articles were then checked by the same two authors to consider the fit with eligibility criteria. A third reviewer (LD) revised any differences in opinion to make a final decision. An electronic database was designed to store all relevant data. Data were extracted separately by two investigators (ODV and LS). In the case of disagreement, LD cross-examined doubtful data. The selection process is shown in Fig. 1. The following data were extracted: first author, year of publication, country of

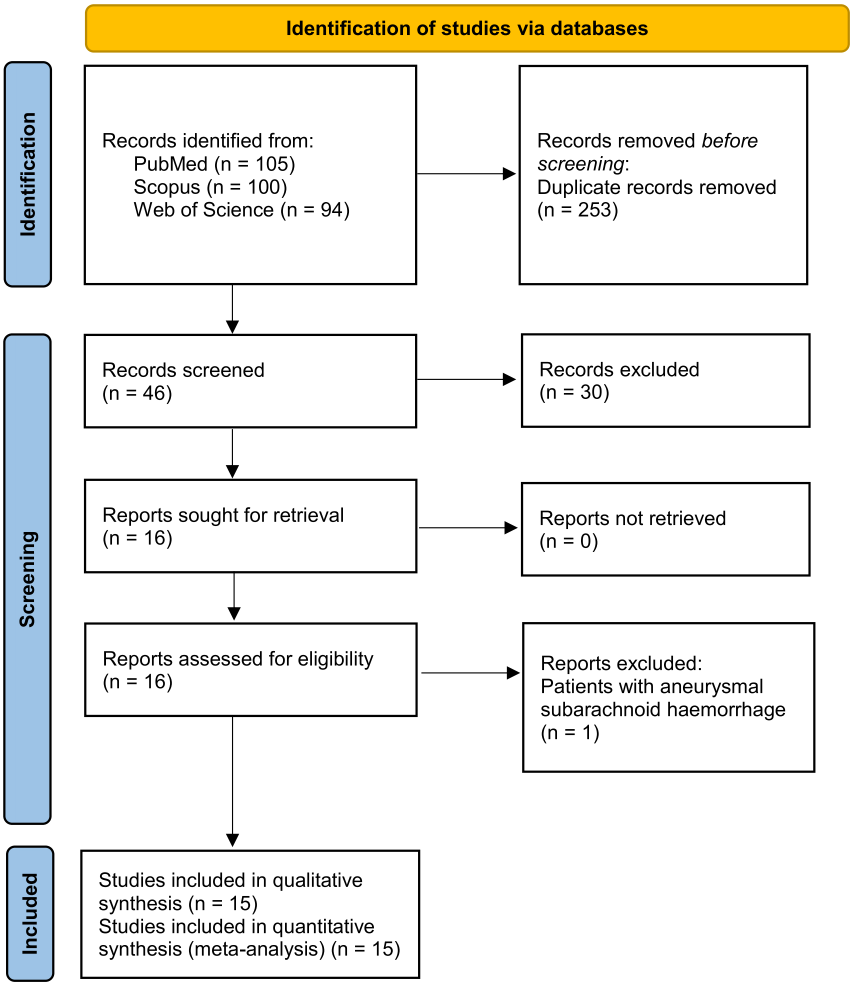

Figure 1 Flowchart on the search and selection of articles included.

origin, type of study and subjects, study design, sample, age, prevalence of malnutrition according to CONUT score, cut-off for high CONUT score, information concerning outcomes of interest and follow-up (see also Table 1). Statistical adjustments used in assessing the relationships between CONUT and outcomes (multivariate analysis) are reported in Supplemental Table 2.

2.3. Risk of bias

The risk of bias of the studies included in the meta-analysis was assessed according to established criteria by the Newcastle-Ottawa Scale (NOS), with the NOS score greater than 6 being considered as "high-quality" [24]. The above data extraction and quality assessment were performed by two authors independently (ODV and GB). Disagreements were solved discussing together.

2.4. Statistical analysis

Odds ratios (ORs) and hazard ratios (HRs) were extracted from the selected publications, and their standard errors (SEs) were calculated from the respective 95% confidence intervals (CIs). The value from each study and the corresponding SE were transformed into their natural logarithms to stabilise the variances and normalise their distribution. If these data were not available, OR and its 95%CI were calculated using the formula: OR: (De/He)/(Dne/Hne), where D: disease; H: healthy; e: exposure and ne: not exposure. The pooled OR (and 95% CI) and HR were estimated using a random-effect model by the DerSimonian and Laird method [25]. The influence of the individual cohorts or a particular study was estimated by sensitivity analysis. The Cochrane Q test and the I^2 statistic were used to evaluate statistical heterogeneity across the studies. Funnel plots were constructed and visually assessed for possible publication bias. Egger's and Begg's tests were also used to explore potential publication bias. In the case of significant funnel plot asymmetry, the pooled estimate was recalculated based on the estimated number of "missing" studies by the "trim-and-fill" method.

Moreover, only for the disability risk, a meta-regression analysis was used to identify associations between outcome risk and relevant study or patients' characteristics as possible sources of heterogeneity.

Table 1 Studies investigating the relationships of the CONUT score with selected outcomes (mortality, disability and infections) in patients with stroke included in the present meta-analysis.

First author	Year	Country	Type of study and subjects	Study design	Sample (M/F)	Age[a]	Prevalence of significant risk of malnutrition[b]	Quality score	Outcomes	Follow-up
Naito	2018	Japan	Single-centre Consecutively hospitalised pts with AIS	Retrospective	264 (171/93)	71 ± 12	18.2% (score ≥5)	9	D (OR)[c] Adjusted	3-mo after stroke onset
Lopez Espuela	2019	Spain	Single-centre Consecutively hospitalised pts with AIS (86%) and AHS (14%)	Prospective	164 (84/80)	77.7 ± 7	10.4% (score ≥5)	8	M (HR) Adjusted	3-mo after stroke onset
Cai	2020	China	Multi-centre Consecutively hospitalised pts with AIS	Prospective	572 (185/387)	Mean 68.7	10.3% (score ≥5)	8	M (OR) I (OR)[c] D (OR) Not adjusted	3-mo after discharge
Naito	2020	Japan	Multi-centre Consecutively hospitalised pts with AIS	Retrospective	1518 (947/571)	NR	7.6% (score ≥5)	9	D (OR)[c] Adjusted	3-mo after stroke onset
Shiga	2020	Japan	Single-centre Consecutively hospitalised pts with AIS	Retrospective	195 (124/71)	72.5 ± 10.5	10% (score ≥5)	8	D (OR) Adjusted	3-mo after stroke onset
Xiang	2020	China	Single-centre Hospitalised pts with AIS	Retrospective	405 (195/210)	66.0 ± 16.0	8.5% (score ≥5)	9	D (OR)[c] Adjusted	3-mo after stroke onset
Zhang	2021	China	Multi-centre Consecutively hospitalised pts with AIS	Prospective	593 (356/237)	67.3 ± 12.0	9.9% (score ≥5)	8	M (OR) D (OR)[c] Adjusted	3 and 12-mo after discharge
Akimoto	2021	Japan	Single-centre Consecutively hospitalised pts with AIS	Retrospective	218 (137/81)	Median 77 (65–99)	10% (score ≥5)	6	D (OR)[c] I (OR)[c] Not adjusted	at discharge (median 26 days)
Hao	2021	China	Single-centre Consecutively hospitalised pts with AIS	Prospective	AIS 791 (418/373) Controls 288 (129/159)	AIS median 82 (78–85) Controls median 81 (78–85)	8.1% (score ≥5)	7	M (OR) I (OR)[c] Adjusted	during hospitalisation
Shiga	2022	Japan	Single-centre Consecutively hospitalised pts with AHS	Retrospective	721 (449/272)	69.2 ± 14.1	4.6% (score ≥5)	9	D (OR) Adjusted	3-mo after stroke onset
Yuan	2021	China	Single-centre First-ever pts with AIS	Prospective	1065 (710/355)	Median 71 (67–75)	8.1% (score ≥5)	9	M (HR) Adjusted	Median 4.74 (3.73–5.82) y
Luo	2022	China	Single-centre Consecutively hospitalised pts with AIS	Retrospective	418 (230/188)	Median 70 (59–78)	12.9% (score ≥5)		D (OR)[c] Adjusted	3-mo after stroke onset

Zhu	2021	China	Multi-centre Consecutively hospitalised pts with AHS	Prospective	328 (219/109)	60.4 ± 12.8	52.4% (score ≥2)	8	M (OR)[c] Not adjusted D (OR) Adjusted I (OR)[c] Not adjusted	3-mo after discharge
Tang	2022	China	Multi-centre Hospitalised pts with AIS	Retrospective	979 (623/356)	66.8 ± 13.2	10 (score ≥5)	8	M (OR) Adjusted	3-mo after stroke onset
Zhang	2022	China	Multi-centre Cohort of pts with AIS	Prospective	8698 (5992/2706)	62.3 ± 11.3	6% (score ≥5)	9	M (HR) D (OR) Adjusted	12-mo after stroke onset

SD = standard deviation; n = number; M = males; F = females; AIS = acute ischemic stroke; AHS = acute haemorrhagic stroke; SAH = subarachnoid haemorrhage; pts = patients; D = disability; M = mortality; I = infections; OR=Odds ratio; HR=Hazard ratio; mo = months; y = years.

Adjusted and not adjusted for other variables of interest (Supplemental Table 2).

[a] Mean ±standard deviation if not otherwise indicated.

[b] Cut-off point for CONUT score in brackets.

[c] Recalculated from available data.

The statistical analyses were performed using the Stata Corp. software (version 11.2; College Station, Texas, USA).

3. Results

3.1. Study selection

A total of 299 articles were identified through the initial literature search (Fig. 1). After removing duplicates (n = 253), 30 studies were excluded by screening titles and abstracts because they did not fulfil the inclusion criteria. The full text of the remaining 16 potentially relevant studies was examined, and one was excluded because it involved only patients with aneurysmal subarachnoid haemorrhage. Thus, 15 studies were considered appropriate and suitable for the present systematic review.

3.2. Study characteristics

The main characteristics of the selected studies (published from 2018 to 2022) are summarised in Table 1. Data on 16 929 subjects were taken into consideration (10 840 men and 6089 women). The studies were carried out in Asia, with the exception of one in Europe [12]. The mean/median age ranged from 60 [20] to 82 years [19].

Table 1 indicates that 12 studies included AIS, 2 AHS and 1 AIS plus a low proportion of patients with AHS. In one study [19], AIS was compared with control hospitalised patients admitted to a hospital for other diseases, while in another study [10], CONUT score was evaluated separately for AIS subtypes (small-vessel occlusion, large-artery atherosclerosis, cardioembolic stroke and other aetiology). Biochemical parameters for deriving CONUT score were assessed within 24 [14,16–18,21,22,26] or 48 h [2,10–12,15,19,20] after admission.

Five papers [14,15,17,21,22] reported data on four CONUT categories (see above), three [2,18,26] subdivided patients into three groups with score 0–1 (normal), 2–4 (light) or ≥5 (moderate/severe), in six papers [10–13,16,19], patients were subdivided into two groups with a score <5 (no risk of malnutrition) or ≥5 (at a risk of malnutrition), whereas in one study [20], a cut-off of 0–1 vs ≥ 2 was used.

The proportion of patients with a moderate/severe risk of malnutrition (high CONUT score ≥5, Table 1) ranged from 4.6 to 18.2% with a negligible percentage with a score 9–12, whereas a high prevalence (41–53%) of light risk was observed in eight studies [2,14,16–18,21,22,26].

3.3. Study quality

As for multicentre and single-centre studies selected (Table 1), the sample size was below 500 subjects in seven, between 500 and 1000 in four and above 1000 subjects in four. The Newcastle-Ottawa quality assessment scale [24] evaluated all the included studies as high-quality with a total score ≥6, as shown in Supplemental Table 1.

3.4. CONUT score and mortality risk

The characteristics of the 7 studies regarding mortality (5 with adjusted data, 12 399 participants and 670 deaths) are given in Table 1. Compared with those admitted to hospital for other diseases, one paper [19] showed that patients with AIS had higher CONUT scores and in-hospital mortality (+8.0%) and also longer lengths of hospital stay (LOS). In that paper, a CONUT score ≥ 5 emerged as a predictor of greater mortality during hospitalisation (OR = 3.77; 95% CI 1.55 to 9.16, $p < 0.001$) [19].

In the long term, three studies showed that the CONUT score was lower in survivors than in non-survivors after stroke [12,18,21]. Data on the association between CONUT score (as a categorical variable) and mortality rate are summarised in Table 1 and Fig. 2, in most cases after adjustment for covariates (Supplemental Table 2). A trend toward a direct association was detected in all the studies included, being statistically significant in three of them (Fig. 2). The meta-analysis confirmed that a CONUT score ≥ 5 was a predictor of mortality in the analyses on AIS carried out separately for OR or HR (Fig. 2). A positive but non-significant trend was also observed in the only study on patients with AHS [20] (Fig. 2).

On the other hand, no increased risk emerged when the light risk category (CONUT score 2–4) was compared with no risk (score 0–1) in terms of both OR (1.37; 95% CI = 0.85 to 2.22, p = 0.19; heterogeneity: p = 0.89, $I^2 = 0\%$) [2,18,22] and HR (0.95; 95% CI = 0.74 to 1.22, p = 0.71; heterogeneity: p = 0.23, $I^2 = 31\%$) [17,21].

An exploratory pooled analysis on all studies was also performed, with an estimated effect = 2.49; 95% CI = 1.74 to 3.56, $p < 0.001$ and a moderate heterogeneity among studies: $I^2 = 40\%$, p = 0.13. Visual analysis of the funnel plot indicated a little asymmetry (Supplemental Figure 1), which was confirmed by formal tests (Egger: p = 0.9, Begg: p = 0.9). Moreover, the “trim-and-fill” method did not identify potentially missing studies. Sensitivity analysis showed that the risk of mortality did not vary substantially with the exclusion of one study at a time.

3.5. CONUT score and disability

Data on the relationship between CONUT score and disability were reported in 10 studies that used the modified Rankin Scale (mRS, score ranging from 0 = no abnormalities to 6 = death) to assess the degree of disability/dependence in activity of daily living (ADL). Six studies showed a higher CONUT score, and therefore a greater risk of malnutrition, in the patients with poor functional outcomes (mRS ≥ 3) [10,11,14,15,18,26]. For the meta-analysis, 10 studies (13 cohorts, with adjusted data in 11) and 5232 participants were included (Fig. 3). A direct association between CONUT score and mRS was observed in 12 cohorts, which was significant in 10 of them, whereas a non-significant opposite trend was observed in one cohort. The meta-analysis revealed that CONUT score (either as a categorical or a continuous variable) was associated with mRS in patients with AIS; this was true also in the two studies concerning AHS (Fig. 3). These

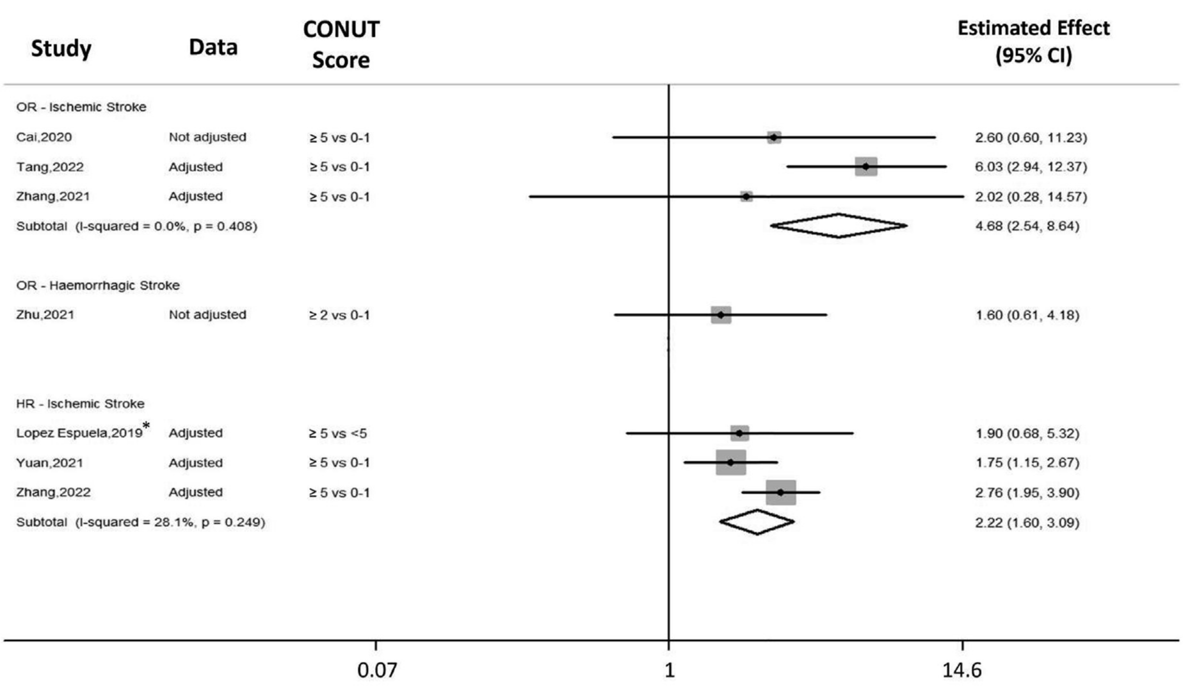

Figure 2 Forest plot of the predicting role of the CONUT score on mortality risk. Legend: Results are expressed as the OR or HR and 95% CI. Squares indicate study-specific risk estimates (size of the square reflects the study-specific statistical weight); horizontal lines indicate 95% CI; the diamond indicates the overall risk with its 95% CI. *In the study by Lopez Espuela et al., only 14% of patients had haemorrhagic stroke.

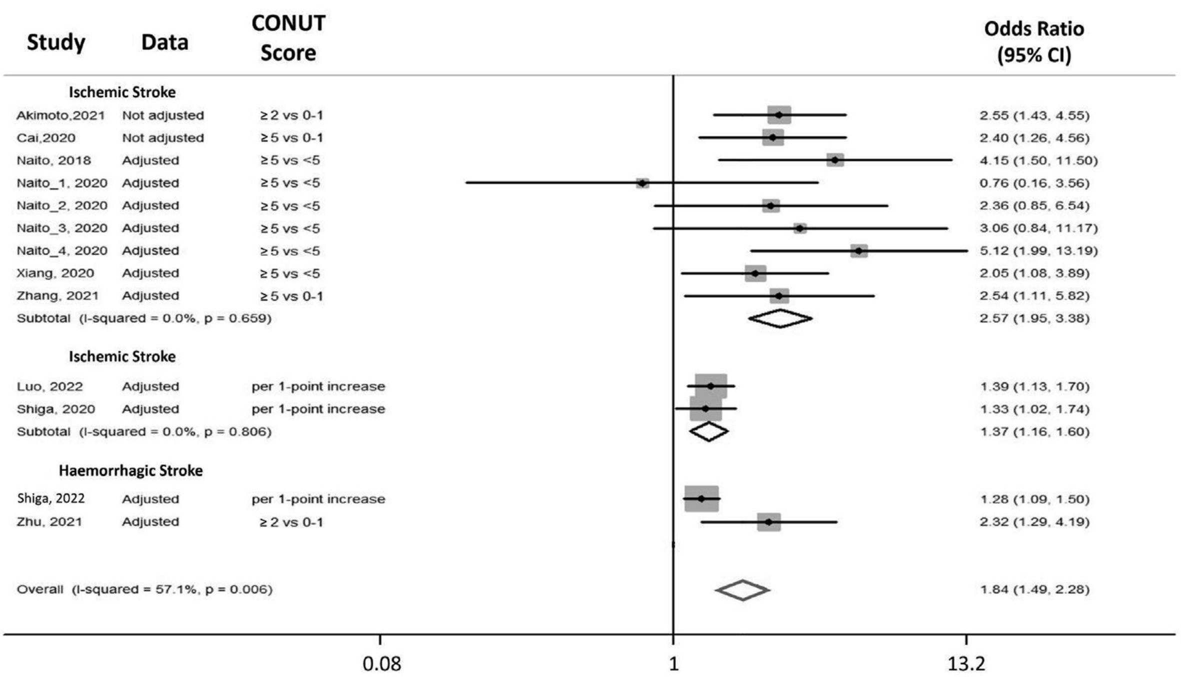

Figure 3 Forest plot of the predicting role of the CONUT score on disability (mRS). Legend: Results are expressed as the OR or HR and 95% CI. Squares indicate study-specific risk estimates (size of the square reflects the study-specific statistical weight); horizontal lines indicate 95% CI; the diamond indicates the overall risk with its 95% CI. Naito_1, 2020 = patients with small-vessel occlusion; Naito_2, 2020 = patients with large-artery atherosclerosis; Naito_3, 2020 = patients with cardioembolic stroke; Naito_4, 2020 = other aetiology patients.

results are confirmed in one study over a 12-month follow-up (OR = 2.25; 95% CI = 1.75 to 2.90, $p < 0.001$) [17]. An increased risk also emerged when CONUT score of 2–4 (light risk of malnutrition) was compared with the CONUT score of 0–1 (OR = 1.70; 95% CI = 1.21 to 2.39, p = 0.002; heterogeneity: p = 0.68, $I^2 = 0\%$) [2,18].

In the exploratory pooled analysis on 13 cohorts, higher CONUT score at baseline was significantly associated with a higher risk of poor functional outcomes (Fig. 3), with significant heterogeneity among studies. Visual analysis of the funnel plot indicated asymmetry (Supplemental Figure 2), as confirmed by Egger's test (Egger: p = 0.01, Begg: p = 0.5). The "trim-and-fill" method identified five potentially missing studies, modifying the pooled estimate to an OR of 1.51 (95% CI = 1.21 to 1.89; $p < 0.001$). Sensitivity analysis showed that the risk of poor functional outcomes did not vary substantially with the exclusion of one study at a time.

Finally, the meta-regression analysis did not detect age, sex, total number of participants, year of publication, prevalence of high CONUT scores and score for risk of bias as significant sources of heterogeneity ($p > 0.05$).

3.6. *CONUT score and infection (development)*

Four studies (total participants n = 1909, three on AIS and one on AHS) assessed the association between CONUT score and infections during hospitalisation (Table 1), all reporting data not adjusted for confounding factors. In three studies, CONUT score was significantly associated with total infection [2,19,20] (OR = 2.18; 95% CI = 1.36 to 3.50, $p < 0.01$), without significant heterogeneity (p = 0.23, $I^2 = 32\%$, Supplemental Figure 3). Additional analyses for type of infection (no evidence of heterogeneity, $p > 0.1$) showed a significant association of CONUT score with pneumonia (OR = 3.68; 95% CI = 1.46 to 9.27, p = 0.006) but not with urinary tract (OR = 1.84; 95% CI = 0.90 to 3.76, p = 0.09) [2,26].

4. Discussion

The present systematic review and meta-analysis investigated the association of CONUT score with different clinical outcomes in patients with stroke. A CONUT score ≥5 was used as a cut-off for moderate/severe risk of malnutrition in a large majority of studies. The most remarkable evidence is that the CONUT score is an independent prognostic factor of mortality. Also, CONUT score was directly associated with disability and infection development. So far, evidence is more consistent in AIS with only a few data in AHS patients.

The assessment of nutritional risk plays a key role in the clinical evaluation of patients with stroke but often does not receive the attention it deserves; actually, in the acute phase and/or in the long term, a strong association has been found between malnutrition and poor outcomes such as dysphagia, infection, complications, greater LOS, hospitalisation costs, disability and mortality [1].

Nutritional status may be evaluated by means of various tools/sets of criteria that intend to identify patients at risk of malnutrition (screening) or produce a diagnosis of malnutrition. In the case of stroke, a wide variability in the prevalence of the risk of malnutrition/malnutrition has been observed, possibly due to differences in diagnostic approach, time point of assessment and type of patients considered [4,5]. Indeed, some tools/sets of criteria cannot easily be applied in patients with stroke (especially in the acute phase) because of the difficulties in gathering proper information such as those on recent weight changes or body composition [5]. Therefore, in the clinical setting, much interest is now focused on instruments that require simple information such as basic haematological and biochemical parameters.

The CONUT score, which is calculated from serum/plasma albumin and total cholesterol plus lymphocyte count (score 0–12), has been proposed as a tool for nutritional screening, for instance, in patients with cancer [7] and can also be used in retrospective studies. Bearing in mind that these three haemato-biochemical tests may be affected by the disease itself and/or by comorbidities, each of them has been related to functional outcomes in patients with stroke [21].

In the present meta-analysis, the association of CONUT score with mortality, disability and infection rate was evaluated based on the available literature. Few data also suggested that the CONUT score is a predictor of LOS [19] as well as of early neurological deterioration [27].

The high mortality observed in patients with stroke in the first few months after stroke onset is commonly associated with malnutrition [1]. Focusing on the predictive role of the CONUT score, seven studies were included in this meta-analysis (Fig. 2), all with blood sampling within 24 or 48 h after stroke onset. Patients at risk of malnutrition have been defined as those with a CONUT score $\geq$5 in a large majority of studies [20]. The most convincing evidence generated by this study was that CONUT score is a predictor of mortality in patients with AIS after stroke onset/discharge (Fig. 2) [2,17,18,21,22]—in most studies over a 3-month follow-up—and this was also true after adjusting for confounders (Fig. 2). On the other hand, there is only one paper on AHS [20], which in addition used an unusual cut-off point of 2 for identifying patients at risk of malnutrition. For completeness of analysis, we performed a pooled analysis, according to the idea that ORs and HRs might be deemed equivalent in this context [28], that confirmed an increased risk associated with higher CONUT scores. These findings were also supported by one study concerning mortality during hospitalisation [19] and one study concerning disability over a 12-month follow-up [17]. Of note, one of the included studies (significant positive association) was carried out in patients submitted to intravenous thrombolysis [22]. The findings of the present paper are in line with previous papers showing that a high CONUT score was a prognostic factor of poor overall survival in patients with different types of cancer [29–35], coronary artery disease [8], acute heart failure [9] and COVID-19 [36]. Lastly, it should be mentioned that some of the selected studies found that also other nutritional tools were predictive of mortality in the same groups of patients with stroke; it was the case of GNRI [17,21,22], PNI [17,21,22], MNA [12] and NRS-2002 [2].

Disability and infection rate have also been related to nutritional status in patients with stroke. Most survivors have residual impairments, such as hemiparesis, spasticity, cognitive dysfunction and aphasia, which lead to activity limitations; disability is commonly appraised using the mRS, which measures the degree of disability/dependence in the daily activities. A total of 10 studies and 13 cohorts were included in this meta-analysis [2,10,11,14–18,20,26]. A direct association between CONUT score and disability (assessed by mRS) was observed in 12 cohorts, which was significant in 10 of them (including the two on AHS), whereas a non-significant opposite trend was observed in one cohort. According to the meta-analysis, an increased risk (CONUT score as a categorical or a continuous variable) clearly emerged for AIS (11 cohorts) (Fig. 3); similar conclusions were reached in the two studies concerning AHS, as well as in patients submitted to intravenous thrombolysis [37] (Fig. 3), and also in patients with aneurysmal subarachnoid haemorrhage [38]. Since mRS also takes into consideration patients who have died (score 6), based on the available data, it is not possible to assess the degree of disability in the survivors. Once again, some of the selected studies found that other nutritional tools were predictive of disability in the same groups of patients; it was the case of GNRI [10,15,17,22,26] or PNI [16,17]. Of note, in another paper [13], the independence in ADL was assessed in patients with stroke using the Functional Independence Measure (FIM) tool, which includes a motor domain and a cognitive domain; the CONUT score on admission was an independent predictor of poor motor (but not cognitive) FIM gain during hospitalisation.

Concerning the comorbidities of stroke, infection is commonly observed in patients with AIS (during hospitalisation and after discharge) with a deleterious impact on clinical outcomes [39]; along with brain inflammation, stroke also leads to immunosuppression, and stroke-induced leukopenia predisposes patients to opportunistic infections, potentially leading to pneumonia or urinary tract infections with a worsened stroke outcome [39]. Previous studies showed that malnutrition is associated with the development of pneumonia and/or urinary tract infections [19,40]. We retrieved four studies that have examined the association of CONUT score with infection during hospital stay, whereas no data are available over the post-discharge period. A significant association has emerged between CONUT score with total infection development without significant heterogeneity among studies (data unadjusted for confounding factors). Evidence is more consistent for AIS and only preliminary for AHS (in this study, an unusual cut-off of $\geq$2 was used to define the risk of malnutrition).

In this meta-analysis, a reasonable number of studies were retrieved, which in all cases but one indicated a CONUT score $\geq$5 to define a moderate/severe risk of malnutrition. No heterogeneity among studies was detected in most cases. However, some limitations should be addressed. First, most of the included studies were single-centre and retrospective. Second, most of patients (except for one paper) were from Asia (China and Japan), and this may limit the application of our results on other countries and ethnic groups. No information is available on changes in CONUT score over hospitalisation or on CONUT score at discharge.

Only in 4 studies out of 15 multivariate analysis included statin use (Supplemental Table 2). Indeed, since statins are expected to reduce the level of total cholesterol down to normal but not very low levels, the effect on CONUT score might be limited. All the four studies reported a significant association with the outcome, and the association of CONUT with the outcome did not change substantially when these data were excluded from the statistical analysis.

In conclusion, being at risk of malnutrition negatively affects clinical outcomes and mortality in patients with stroke, with much more consistent evidence in AIS. Continuous monitoring of the nutritional status and improved nutritional management are needed to ameliorate clinical course and recovery after stroke. The findings of this meta-analysis indicate that CONUT score is a valuable prognostic factor of survival, disability and infection development after stroke. Larger-scale international multicentre prospective studies are needed to further validate these findings.

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Author contributions

Conceptualization: ODV, LS, FP. Data curation: ODV, GB. Formal analysis: ODV, LD. Methodology: ODV, LD. Writing – original draft: ODV, LD, LS. Writing – review and editing: FP.

Declaration of Competing Interest

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2023.05.012.

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