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Association of nutritional indices and prognosis of stroke patients: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: The aim of this study was to document the association between malnutrition and mortality as well as functional outcomes in patients with stroke.

MATERIALS AND METHODS: PubMed, Embase and Scopus databases were systematically searched for observational studies that had used either of the three nutritional indices, geriatric nutritional risk index (GNRI), prognostic nutritional index (PNI), and controlling nutritional status score (CONUT), and examined the association between malnutrition and outcomes of interest in patients with stroke. The primary outcome was mortality and secondary outcomes were risk of recurrence and functional disability. Analysis was performed using STATA 16.0 software (College Station, TX, USA) and pooled effect sizes were reported as either hazards ratio (HR) or as odds ratio (OR). Random effects model was used for the analysis.

RESULTS: A total of 20 studies were included, of which, 15 were focused on acute ischemic stroke (AIS) patients. Among patients with AIS, moderate to severe malnutrition, assessed using CONUT (OR 4.80, 95% CI: 2.31, 9.98), GNRI (OR 3.57, 95% CI: 2.08, 6.12) and PNI (OR 8.10, 95% CI: 4.69, 14.0), was associated with increased risk of mortality within 3 months and at 1-year follow-up (CONUT: OR 2.74, 95% CI: 1.96, 3.83; GNRI: OR 2.26, 95% CI: 1.34, 3.81; PNI: OR 3.32, 95% CI: 2.24, 4.93). Patients with moderate to severe malnutrition, assessed using any of the three indices, had an increased risk of having an unfavourable outcome [modified Rankin Score (mRS) score of 3 to 6, denoting major disability and/or death] within 3 months and at 1-year follow-up. Only one study reported the risk of recurrence.

CONCLUSIONS: Assessing malnutrition in stroke patients at the time of hospital admission using any of the three nutritional indices is useful due to the observed association of malnutrition with survival and functional outcomes. However, due to a limited number of studies, there is a need for large prospective studies to validate the findings observed in this meta-analysis.

Key Words:
Stroke, Ischemic, Malnutrition, CONUT, GNRI, PNI, Mortality, Recurrence, Functional Outcome, Modified Rankin Scale, Meta-analysis.

Introduction

Stroke is one of the common causes of mortality and functional disability among adults worldwide[1]. An increasingly large proportion (>85%) of patients with stroke have underlying ischemic disease and these patients are at a high risk of recurrence[1,2]. Recurrent episodes of stroke are often more severe than the primary event and lead to further loss of functional capacity[3,4]. Therefore, early identification of the risk factors to prevent further episodes and potentially reduce the risk of mortality and disability is crucial.

Malnutrition in stroke patients is one of the common risk factors that has been shown[5,6] to be associated with unfavorable outcomes, such as mortality and functional disability. Recent evidence[7] suggests that the prevalence of malnutrition in stroke patients, when assessed at the time of admission, ranges from 6 to 62%, based on the nutritional assessment tool used. Therefore, it is imperative to perform early screening for nutritional status of the patient at the time of hospital admission, and to establish timely and effective nutritional management. The conventional tools for investigation of the nutritional status are time-consuming and require subjective assessments which may be challenging in patients with stroke[8]. A pragmatic approach of nutritional assessment should use objective, easy to measure parameters and hematological parameter-based indices. Such commonly used indices are the controlling nutritional status (CONUT) score (which

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includes serum albumin, total cholesterol levels and lymphocyte count in peripheral blood), prognostic nutritional index (PNI) score (includes serum albumin and total lymphocyte count), and geriatric nutritional index (GNRI) (includes serum albumin and body weight)[9,10]. These assessments utilize routine blood-based parameters. Numerous studies[11-14] confirmed the prognostic significance of these methods, as well as their association with clinical outcomes in patients with gastrointestinal, urinary tract and lung cancers and cardiovascular diseases.

A recent meta-analysis by Mehta et al[15] aimed to identify the relationship between nutritional indicators and outcomes in stroke patients. They found that underweight patients (based on body mass index, BMI) had an increased risk of long-term mortality. In contrast, patients with normal BMI, and overweight and obese patients had a decreased risk of long-term mortality. Moreover, the risk of mortality decreased in patients with high serum albumin level[15]. The meta-analysis[15] also included studies[15-17] that had assessed malnutrition using Subjective Global Assessment (SGA) tool or Malnutrition Universal Screening Tool (MUST) and found that patients who were malnourished had higher risk of all-cause mortality and poor functional outcome. In addition, studies that used anthropometric indicators for nutritional status assessment such as mid-upper arm circumference (MUAC), waist circumference, waist hip ratio and triceps skin fold thickness were also included in the review[15]. The aim of our meta-analysis was to specifically investigate whether objective, easy to measure and commonly used nutritional assessment indices i.e., CONUT, PNI and GNRI can predict outcomes in stroke patients. We believe that such contemporary evidence is required to make a case for incorporation of these assessment tools in the routine clinical care for stroke patients. The primary outcome of interest for our study was mortality. Secondary outcomes were risk of recurrence and functional disability.

Materials and Methods

Search Strategy and Databases Searched

Literature search was performed in databases, including PubMed, EMBASE and Scopus, to identify eligible English language studies that were published until 30th September 2022. We used the following search terms to identify potentially eligible studies: "(controlling nutritional status score OR CONUT OR prognostic nutritional index score OR PNI OR geriatric nutritional risk index score OR GNRI OR nutritional indices) AND (stroke OR ischemia stroke OR ischaemic stroke OR hemorrhagic stroke OR haemorrhagic stroke OR cerebrovascular risk) AND (survival OR mortality OR functional outcome OR recurrence OR clinical outcome)". This review was registered in PROSPERO (registration number CRD42022363410). We followed the standard PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[18].

Study Selection and Data Extraction

Studies that were done in patients with stroke and had looked at the association between nutritional status at the time of hospital admission with the outcomes of stroke were included. More specifically, we were interested only in three nutritional indices i.e., CONUT, GNRI and PNI. We did not restrict our selection of studies to only a specific type of stroke. Therefore, studies with patients having acute ischemic stroke or acute hemorrhagic stroke or a combination of both were eligible to be included. To be considered eligible for inclusion in this meta-analysis, the studies must have reported on results that are relevant to the outcomes of interest. The primary outcome of interest was risk of mortality. Secondary outcomes of interest were risk of disability (functional outcome) and risk of recurrence.

Two review authors (LH, MZ) independently screened the titles and abstracts to identify the relevant citations, followed by full text review. The data were extracted using a pre-tested sheet comprising of variables related to study identifier, design, participants characteristics, sample size and key outcome effects. Any disagreements or discrepancies between reviewers were resolved by discussions or by referring to a third review author (YY).

Statistical Analysis

Analysis was performed using STATA 16 software (College Station, TX, USA). Pooled effect sizes were reported as hazards ratio (HR) or as odds ratio (OR), with 95% confidence interval (CI). We decided to use the random effects model, using the Restricted Maximum Likelihood Method (REML), as the included studies differed in their methodology (e.g., duration of follow up, stroke management, age of participants, baseline clinical characteristics and study setting). These differences were bound to create substantial heterogeneity and therefore, random effects model was considered for the analysis[19]. Publication bias was assessed using Egger's test[20]. Assessment of the risk of bias was done using the Newcastle-Ottawa Scale[21]. A *p*-value lower than 0.05 was considered to denote statistical significance.

Results

Study Selection Process and Overview of the Include Studies

Literature search across the databases identified a total of 862 studies. After exclusion of duplicates, 747 studies were screened based on title and abstract. Of them, 683 were excluded. Of the remaining 64 studies, 20 studies[22-41] were eventually included in this meta-analysis (Figure 1). The specific details of the selected studies[22-41] are presented in **Supplementary Table I**. A total of 11 studies were retrospective[22,26,29,30,32,34,37-41] and 9 studies were prospective in design[23,24,25,27,28,31,33,35,36]. Majority of studies were conducted in China (n=9)[22,24-29,33,35] and Japan (n=7)[30,34,36,37,39-41]. Remaining studies were done in South Korea[23], Italy[38], Spain[31] and USA[32]. Overall, the studies were done either in upper-middle-income or high-income settings. Most of the studies were done in patients with acute ischemic stroke (AIS) (n=15)[22-30,34,35,37-41]. One study was done in patients with acute hemorrhagic stroke (AHS)[33], one study did not specify the type of stroke[32] and, remaining 3 studies had both AIS and AHS[31,36,40]. Quality assessment using the Newcastle Ottawa scale showed that the included studies[22-41] had a score ranging from 6-9 (out of the maximum attainable score of 9) indicating that they are of good quality (Supplementary Table I).

Mortality Within 3 Months of Follow-Up

Patients with moderate to severe malnutrition, assessed using CONUT (OR 2.82, 95% CI: 1.26, 6.35; N=6, I^2=73.7%) and GNRI (OR 3.57, 95% CI: 2.08, 6.12; N=2, I^2=9.5%), had higher risk of mortality within 3 months of follow-up (Figure 2)

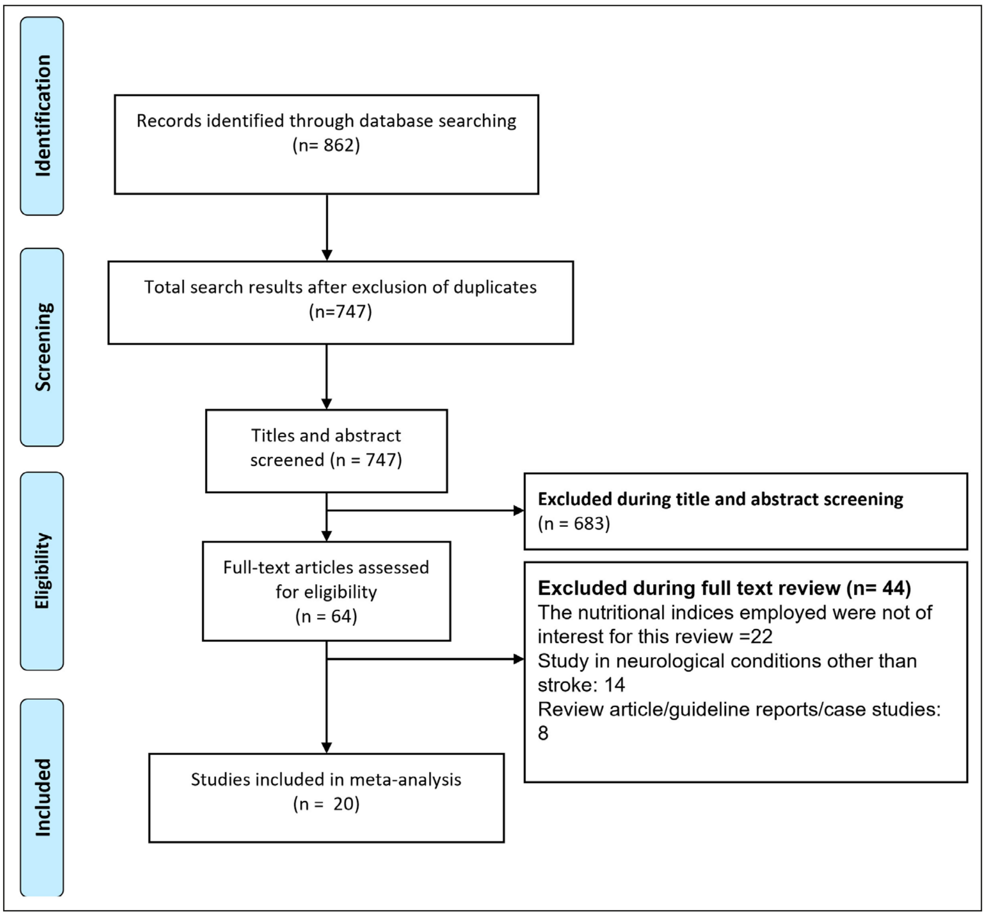

Figure 1. Selection process of the studies included in the review.

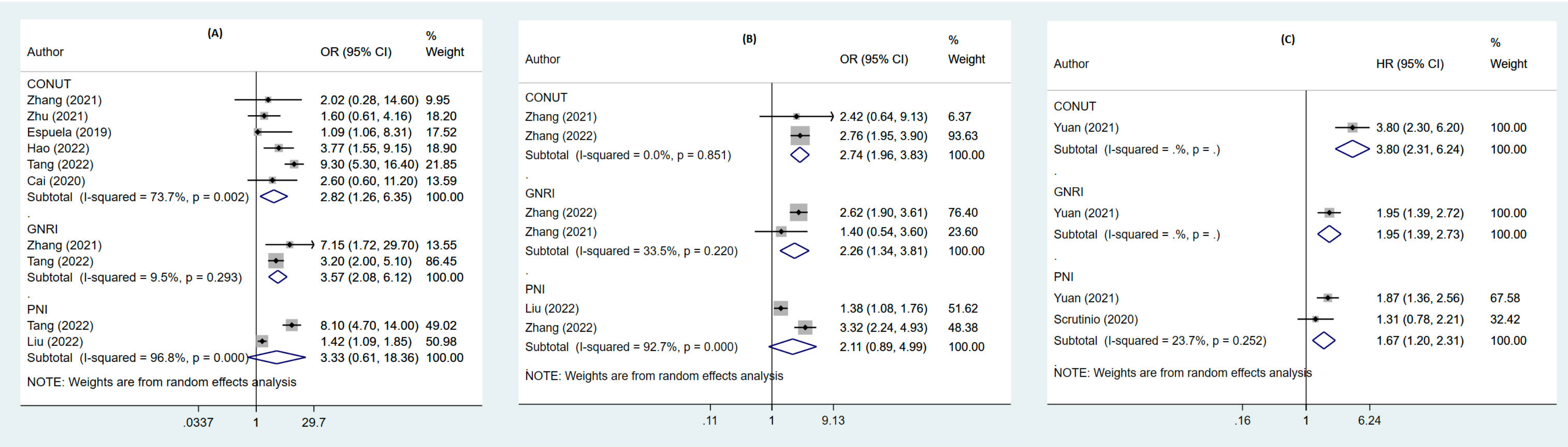

Figure 2. Association between moderate and severe malnutrition and risk of mortality (**A**) within 3 months of follow up (**B**) at 1 year of follow up and (**C**) at more than one year of follow up in patients with stroke.

compared to patients that were not malnourished. The risk was not statistically significant for PNI (OR 3.33, 95% CI: 0.61, 18.36; N=2, I^2=96.8%). There was no evidence of publication bias on Egger's test (p>0.05).

Mortality Within 1 Year of Follow-Up

Patients with moderate to severe malnutrition, assessed using CONUT (OR 2.74, 95% CI: 1.96, 3.83; N=2, I^2=0.0%) and GNRI (OR 2.26, 95% CI: 1.34, 3.81; N=2, I^2=33.5%), had higher risk of mortality at 1 year of follow-up (Figure 2). The risk was not statistically significant for PNI (OR 2.11, 95% CI: 0.89, 4.99; N=2, I^2=92.7%). There was no evidence of publication bias on Egger's test (p>0.05).

Mortality at Follow-Up of More Than 1 Year

Studies[24,38] reporting this outcome had a follow-up period of 4.5 years and 2 years. Moderate to severe malnutrition, assessed by CONUT (HR 3.80, 95% CI: 2.31, 6.24; N=1), GNRI (HR 1.95, 95% CI: 1.39, 2.73; N=1) and PNI (HR 1.67, 95% CI: 1.20, 2.31; N=2, I^2=23.7%), was associated with increased risk of mortality (Figure 2). There was no evidence of publication bias on Egger's test (p>0.05).

Modified Rankin Scale (mRS) Score Within 3 Months of Follow-Up

Compared to subjects without undernutrition, those with moderate to severe malnutrition had increased risk of having a mRS score of 3 to 6 (indicating an unfavorable outcome comprising of major disability and/or death). This was applicable to all the three nutritional indices i.e., CONUT (OR 2.13, 95% CI: 1.48, 3.05; N=9, I^2=84.4%), GNRI (OR 2.10, 95% CI: 1.11, 3.97; N=6, I^2=96.9%) and PNI (OR 2.25, 95% CI: 1.19, 4.25; N=1) (Figure 3). There was evidence suggestive of presence of publication bias (Egger's p-value was 0.04).

Modified Rankin Scale (mRS) Score at One Year of Follow-Up

Patients with moderate to severe malnutrition had increased risk of having a mRS score of 3 to 6. This was applicable to all the three nutritional indices i.e., CONUT (OR 2.19, 95% CI: 1.72, 2.80; N=2, I^2=0.0%), GNRI (OR 1.73, 95% CI: 1.05, 2.86; N=2, I^2=60.7%) and PNI (OR 3.36, 95% CI: 2.33, 4.84; N=1) (Figure 3). There was no evidence of publication bias on Egger's test (p>0.05).

Risk of Recurrence

Only one study by Han et al[29] reported the risk of recurrence. The study observed an increased risk of recurrence in patients with moderate to severe malnutrition that was assessed using CONUT (HR 3.47, 95% CI: 2.22, 5.43; N=1) and PNI (HR 2.78, 95% CI: 2.07, 3.73; N=1) (Figure 4).

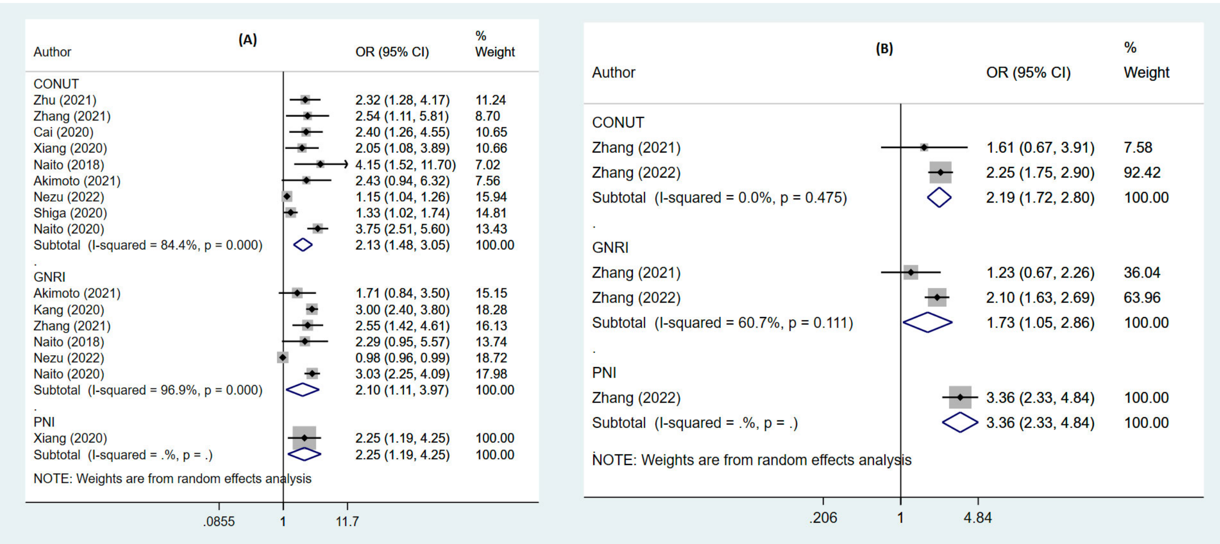

Figure 3. Association between moderate and severe malnutrition and risk of having mRS score of 3 to 6 (**A**) within 3 months of follow up (**B**) at one year of follow up in patients with stroke.

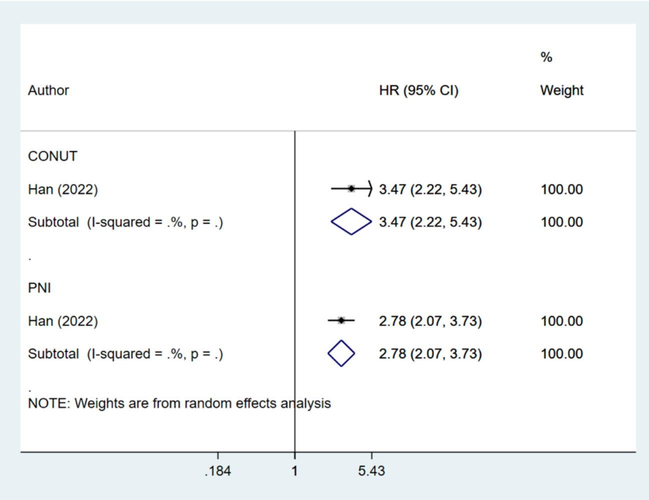

Figure 4. Association between moderate and severe malnutrition and risk of recurrence in patients with stroke.

Discussion

Previous studies[5,42] have already established that malnutrition is associated with poor survival and functional outcomes in patients with stroke. The current review was specifically done to examine whether objective, easy to measure and hematological parameter-based nutritional assessment indices i.e., CONUT, PNI and GNRI can predict outcomes in stroke patients. We found that moderate to severe malnutrition was associated with increased risk of mortality within 3 months and at 1 year of follow-up, and in increased risk of having an unfavorable outcome (major disability and/or death) within 3 months and at 1 year of follow-up.

Studies[43,44] show that activation of catabolic pathways after an event of stroke is due to a variety of causes that comprises of impaired nutritional status, infection, and sarcopenia. Due to a decreased metabolic reserve, the catabolic activation may be more severe in malnourished patients. Numerous studies[45] report better outcome after stroke in obese and overweight patients, the obesity paradox. Underweight patients are at higher risk of being frail, and frailty is shown to be linked[46] to an increased risk of adverse cerebrovascular outcomes.

To understand the nature of the association between the three nutritional indices and the outcomes of stroke, it is important to know the associations of individual components of these indices with the outcomes. Serum albumin measurement is common to all three methods, with values of serum albumin correlating with favorable scores. A recent meta-analysis[15] showed that higher serum albumin led to a 70% decrease in the risk of post-stroke mortality, compared to normal levels (OR of 0.29, with 95% CI of 0.18 to 0.48). The same review also noted that low serum albumin levels were associated with an increased risk of mortality (OR 3.46, 95% CI of 1.78 to 6.74). Previous studies[47,48] have also found evidence for the relation between serum albumin and mortality in adults. There have also been observations[49,50] that low serum albumin is commonly found in association with high levels of inflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor-alpha. Such an inflammatory state not only reduce the albumin synthesis but also leads to its degradation and increased transcapillary leakage[49,50]. The increased mortality and poor functional outcomes in malnourished stroke patients could be, therefore, a result of the direct effect of the high-level inflammatory state[51,52].

In both CONUT and PNI, higher lymphocyte count is linked to favorable scores. There are studies[53,54] that suggest poor prognosis with low lymphocyte count in patients with cardiovascular diseases. Juli et al[55] found that in patients with acute ischemic stroke, lymphocyte depletion is associated with poor survival outcomes. Studies[55] of mice models showed that the increase in lymphocyte count enhances the anti-inflammatory effect of interleukin-10 and at the same time, reduces the effect of pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor-alpha.

Total cholesterol is another component of the CONUT scoring system, with higher levels contributing to favorable score. Studies[56,57] have shown that low total cholesterol leads to unfavorable outcomes in patients with acute ischemic stroke. It is proposed[58] that cholesterol is required for maintaining the normal fluidity of vascular membranes and enhances their resistance to rupture.

Limitations

Our review has several limitations that should be considered while interpreting the findings. First, all the studies were observational in design and therefore, remains a possibility that some important confounders are not adjusted in the model or the data on some important variables is not present, especially in studies with a retrospective design. Another limitation is the differences in the cut-off used by different studies for moderate and severe malnutrition for CONUT, PNI and GNRI (Supplementary Table I). These differences in definitions may lead to some heterogeneity in the results and limit the external generalizability of our findings to some extent. It is important to note that all the studies were done in upper-middle-income or high-income settings. Therefore, the findings could not be extended to other settings. This also limits the wider applicability of the study findings. An additional limitation is that the number of studies reporting certain outcomes was too small for pooled analysis. Therefore, the meta-analysis was unable to provide reliable evidence on these outcomes (such as risk of mortality at 1 year and more of follow-up as well as a risk of recurrence). Future studies should focus on long term outcomes and should be carried with a larger sample size and robust methodology.

Conclusions

Our meta-analysis suggests that nutritional indices such as CONUT, PNI and GNRI could be helpful in the prediction of short-term survival and functional outcomes. However, due to limited number of studies, their association with long term outcomes could not be effectively ascertained. More prospective studies are needed to validate our findings and broaden the evidence base for inclusion of these nutritional indices in routine clinical care of stroke patients.

Authors' Contributions

YY conceived and designed the study, LH and MZ collected data and performed data analysis. LH wrote the draft of this manuscript. YY edited the manuscript.

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Conflict of Interests

The authors declare that there is no conflict of interests.

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Data availability statement

All the data used in the analysis is presented within the manuscript. For further information, specific studies (referenced in the manuscript) could be referred.

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