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Association between nutritional indices and mortality after hip fracture: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: This study analyzed evidence on the association between prognostic nutritional index (PNI), controlling nutritional status (CONUT), geriatric nutritional risk index (GNRI), and mini-nutritional assessment-short form (MNA-SF) and mortality after hip fracture.

MATERIALS AND METHODS: The online databases of PubMed, Scopus, Web of Science, Embase, and Google Scholar were accessed for literature reporting the association between PNI/CONUT/GNRI/MNA-SF and mortality after hip fracture. Data were pooled in a random-effects model.

RESULTS: 13 studies were eligible. Meta-analysis of six studies showed that individuals with low GNRI had a significantly higher risk of mortality as compared to those with high GNRI (OR: 3.12 95% CI: 1.47, 6.61 I^2=87% *p*=0.003). Meta-analysis of three studies found that low PNI was not a significant predictor of mortality amongst hip fracture patients (OR: 1.42 95% CI: 0.86, 2.32 I^2=71% *p*=0.17). On pooling data from five studies, it was noted that patients with low MNA-SF scores had a significantly higher risk of mortality in comparison to those with higher scores (OR: 3.61 95% CI: 1.70, 7.70 I^2=85% *p*=0.0009). Only one study was available on CONUT. Heterogeneity of cut-offs and variable follow-up were important limitations.

CONCLUSIONS: Our results indicate that MNA-SF and GNRI can predict mortality in elderly patients undergoing surgery for hip fractures. Data is scarce on PNI and CONUT to draw strong conclusions. Variation in cut-offs and follow-up period are important limitations which need to be addressed by future studies.

Key Words:
Hip, Trauma, Nutrition, Malnourished, Geriatric, Death.

Introduction

Hip fracture is a common debilitating condition affecting the elderly across the globe[1]. Its incidence varies in different countries, but the condition is predominant in women as compared to men with global estimates of 18% and 6%, respectively[2]. Due to increased life expectancy owing to improved healthcare, the proportion of elderly is bound to increase in the near future. Correspondingly, the annual incidence of hip fractures is also deemed to increase from 1.26 million in 1990 to about 4.5 million in 2050[2]. The importance of the condition stems from the fact that hip fractures are associated with high mortality with one-year rates of 20-40%[3]. Hence, it is necessary that factors influencing mortality are correctly identified so that targeted preventive measures can be undertaken to decrease adverse outcomes.

Malnutrition has been identified as an important and modifiable prognostic factor for several medical conditions[4]. Elderly patients are at particular risk of malnutrition, and it impacts their overall health, physical functioning, and quality of life[5]. Research[6] indicates that around 18.7 to 45.7% of elderly with hip fractures are malnourished at admission and it may adversely affect their outcome. Over the years, several malnutrition indicators have been developed and tested amongst varied population to predict prognosis, however, no single index has found acceptance in the medical community[7]. Earlier singular values like serum albumin, arm circumference, calf circumference, or body mass index (BMI) were commonly used but these could be influenced by confounding factors. Hence, questionnaire-based tools like mini-nutritional assessment-short form

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(MNA-SF) or combination indices like prognostic nutritional index (PNI), controlling nutritional status (CONUT), and geriatric nutritional risk index (GNRI) have been developed[8].

Nevertheless, there is scarce literature on the prognostic ability of these malnutrition indices on outcomes of hip fracture patients. It is unclear which index can predict mortality and which cannot. While there have been individual studies[9-11] describing such association, no systematic review has comprehensively analyzed available evidence on these different indices. Hence, the current review was performed to assess if PNI, CONUT, GNRI, and MNA-SF can predict mortality rates in hip fracture patients.

Materials and Methods

Literature Search

The databases of PubMed, Scopus, Web of Science, and Embase were accessed for articles. The database of Google Scholar was searched for gray literature. The search was carried out by two reviewers independently. All articles published between the inception of the databases to 25th September 2022 were searched but due to translation restrictions, only English-language studies were eligible. The search terms used were: "Prognostic nutritional index", "Controlling nutritional status ", "Geriatric nutritional risk index", "Mini-nutritional assessment", "PNI", "CONUT", "GNRI", "MNA", "hip fracture", "femoral fracture", "nutrition", and "mortality". Search terms were combined with Boolean operators and are shown in **Supplementary Table I**. All search results were examined first by their titles/abstracts to identify studies relevant to the review. The selected full texts were read by the two reviewers independently and any disagreements were resolved by discussion with the third reviewer. A manual search of the referenced studies among the included studies was also conducted. Reporting of the review was done based on the PRISMA statement[12] along with pre-registration of the study on PROSPERO (CRD42022360680).

Inclusion and Exclusion Criteria

All studies carried out on hip fractures patients were eligible. For inclusion, the study had to report the association between PNI, CONUT, GNRI, or MNA-SF and mortality after hip fracture. Outcomes were to be reported as odds ratios (OR), risk ratios (RR), or Hazard ratios (HR) with 95% confidence intervals (CI). Exclusion criteria were: (1) Studies on femoral shaft fractures or not reporting separate data for hip fractures (2) Studies using other versions of MNA and not MNA-SF (3) Studies with a repetitive or overlapping sample.

Data Extraction and Risk of Bias Assessment

Two reviewers were involved in data extraction which included: name of the author, year, study type and location, number of patients, age and gender, diabetes and hypertension, the nutritional index used, cut-off value, number of patients malnourished, management of hip fracture, follow-up, and outcomes.

As all studies were observational, the risk of bias was examined by the Newcastle-Ottawa scale (NOS)[13]. Two reviewers were involved in the process independently and any disagreements were solved by a discussion with the third reviewer. The NOS awards stars for the selection of study population, comparability, and outcomes. These are given a maximum of four, two, and three points, respectively.

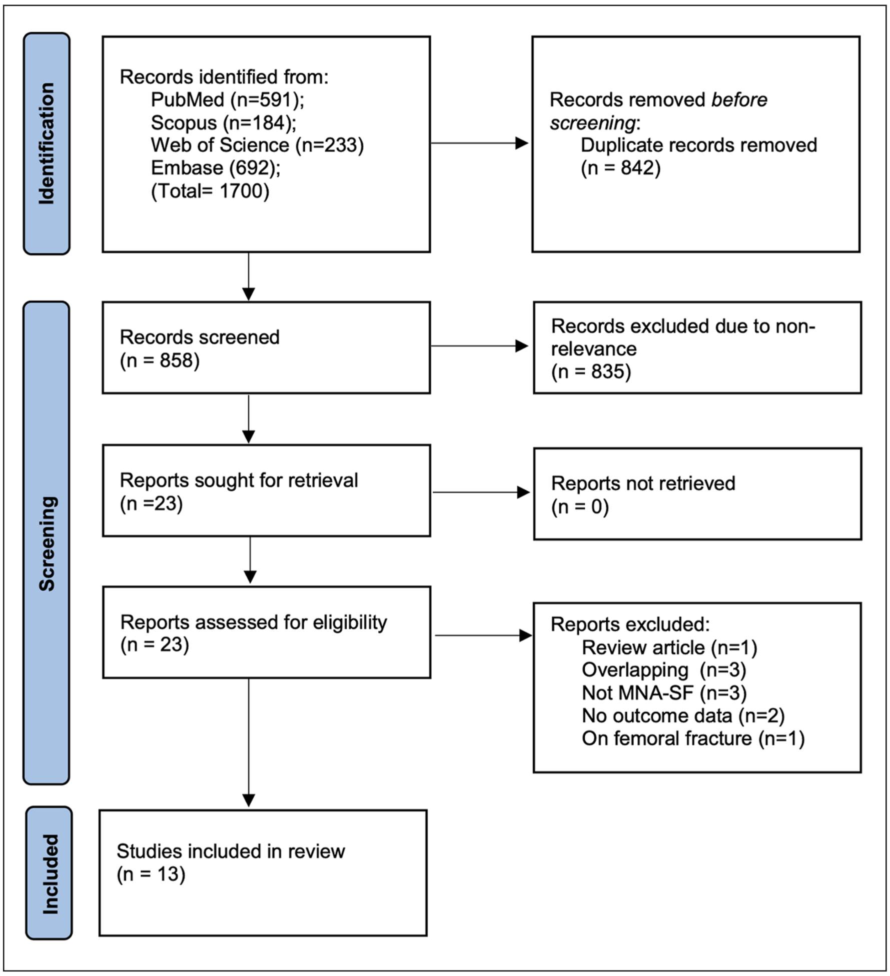
Statistical Analysis

The software "Review Manager" [RevMan, version 5.3; Nordic Cochrane Centre (Cochrane Collaboration), Copenhagen, Denmark; 2014] was used for the meta-analysis. The outcome ratios were combined by the generic inverse variance function. Data was pooled as OR with 95% CI. The random-effects model was chosen. Heterogeneity was assessed using the I^2 statistic. I^2 values of 25-50% represented low, values of 50-75% medium, and more than 75% represented substantial heterogeneity. Since <10 studies were available in the meta-analysis, we did not use funnel plots to assess publication bias. We also conducted a sensitivity analysis wherein individual studies were removed one by one, and the effect size was recalculated.

Results

After the literature search, 1,700 articles were found, of which 842 were duplicates. 858 underwent initial screening and 835 studies were not found relevant to the review. 23 full texts were assessed and 13 met the inclusion criteria[9-11,14-23] (Figure 1).

Figure 1. Study flowchart.



The included studies were published in the past decade (Table I). Studies[9,11,14-17,19,21,23,] were mostly on Asian populations while three[10,18,20] were on European and one on the American population[22]. The sample size ranged from 80 to 1,040. All were cohort studies with five[9,10,17,18,20] using MNA-SF, four[14,15,22,23] using GNRI, two[11,19] using PNI, and the remaining two[16,21] studies using two different nutritional markers each (GNRI and PNI in one study[16] and GNRI and CONUT in another[21]). All patients underwent surgical intervention in the included studies. Patients were classified as malnourished based on preoperative measurements. The included patient population was elderly (mean or median: >75 years) with a predominance of females in all studies. The follow-up duration was variable ranging from one to 36 months. The NOS score of studies ranged from 5-8. Five studies[9,17,20,21,23] had high risk of bias while remaining had moderate risk of bias.

Six studies[14-16,21-23] reported data on GNRI and mortality after hip fractures. The cut-offs used by the studies to classify malnutrition ranged from 75.4 to 92. Meta-analysis showed that patients with low GNRI had a significantly higher risk of mortality as compared to those with high GNRI (OR: 3.12 95% CI: 1.47, 6.61 I^2=87% p=0.003) (Figure 2). The effect size remained significant despite the exclusion of singular studies on sensitivity analysis.

PNI was used in three studies[11,19,16] to classify the patients as nourished and malnourished. The cut-offs for PNI used were 38 or 45. The meta-analysis found that low PNI was not a significant predictor of mortality amongst hip fracture patients (OR: 1.42 95% CI: 0.86, 2.32 I^2=71% p=0.17) (Figure 3). During sensitivity analysis, the removal of the study of Ren et al[19] changed the significance of the results (OR: 1.10 95% CI: 1.01, 1.19 I^2=0% p=0.03).

Five studies[9,10,17,18,20] used MNA-SF to find patients who were malnourished. All studies used a cut-off of 7. On pooling data, it was noted that patients with low MNA-SF scores had a significantly higher risk of mortality compared to those

Table I. Details of included studies.

Study	Country	Sample size	Age (years)	Male gender (%)	DM (%)	HT (%)	Nutritional score	Cut-off used	Malnourished (%)	Manage-ment of hip fracture	Follow-up (months)	NOS score
Liu 2022[16]	China	546	75.2 ± 10.2	31.3	NR	NR	PNI GNRI	45 98	52.9 43.8	Surgery	12	8
Funahashi 2022[15]	Japan	1040	84.7 ± 7.8	23.3	15.9	53.9	GNRI	75.4	8.2	Surgery	1	7
Fujimoto 2022[14]	Japan	108	84 (78-89)	21.3	NR	NR	GNRI	98	NR	Surgery	12	8
Yokoyama 2021[23]	Japan	137	81	21.2	NR	NR	GNRI	92	54.7	Surgery	6	6
Feng 2021[11]	China	221	78± 5	21.2	25.1	49.2	PNI	38	NR	Surgery	45	8
Thorling 2020[10]	Sweden	160	80 ± 10	27.5	11.2	NR	MNA-SF	7	6.2	Surgery	12	8
Hao 2020[22]	USA	290	82 ± 7	27	NR	NR	GNRI	92	11.7	Surgery	2	7
Helminen 2019[20]	Finland	265	84	33.3	NR	NR	MNA-SF	7	7	Surgery	4	5
Kotera 2019[21]	Japan	607	87 ± 6	18.7	13.3	53	GNRI CONUT	92 8	8.6 11.6	Surgery	6	6
Miu 2017[9]	Hong Kong	218	83.5 ± 7.5	33.9	NR	NR	MNA-SF	7	26.1	Surgery	6	6
Ren 2017[19]	China	80	86 ± 5	43.8	42.5	78.8	PNI	38	48.8	Surgery	12	8
Helminen 2017[18]	Finland	594	84	29	NR	NR	MNA-SF	7	7	Surgery	12	8
Koren-Hakim 2016[17]	Israel	215	83.5 ± 6.1	28.4	23.3	69.3	MNA-SF	7	11.6	Surgery	36	6

DM, Diabetes mellitus; HT, hypertension; MI, myocardial infarction; NR, not reported; PNI, prognostic nutritional index; NOS, Newcastle Ottawa scale; OR: Odds ratio; CI, confidence intervals; MNA-SF, Mini nutritional assessment scale short form; GNRI, geriatric nutritional risk index; CONUT, controlling nutritional status.

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Year
Kotera 2019	1.5041	0.459	18.0%	4.50 [1.83, 11.06]	2019
Hao 2020	0.3853	0.6154	14.9%	1.47 [0.44, 4.91]	2020
Yokoyama 2021	2.9976	1.4583	5.4%	20.04 [1.15, 349.26]	2021
Liu 2022	0.3832	0.2287	22.3%	1.47 [0.94, 2.30]	2022
Fujimoto 2022	0.2231	0.0746	24.0%	1.25 [1.08, 1.45]	2022
Funahashi 2022	3.2995	0.5874	15.4%	27.10 [8.57, 85.69]	2022
Total (95% CI)			**100.0%**	**3.12 [1.47, 6.61]**	

Heterogeneity: $Tau^2 = 0.61$; $Chi^2 = 37.53$, df = 5 ($P < 0.00001$); $I^2 = 87\%$
Test for overall effect: Z = 2.97 (P = 0.003)

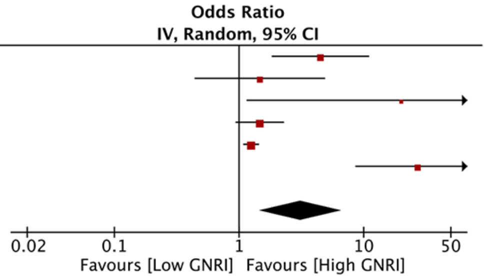


Figure 2. Meta-analysis of association between GNRI and mortality after hip fractures.

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Year
Ren 2017	1.6094	0.6009	13.1%	5.00 [1.54, 16.23]	2017
Feng 2021	0.0862	0.0419	51.3%	1.09 [1.00, 1.18]	2021
Liu 2022	0.2585	0.2369	35.6%	1.29 [0.81, 2.06]	2022
Total (95% CI)			**100.0%**	**1.42 [0.86, 2.32]**	

Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 6.86$, df = 2 ($P = 0.03$); $I^2 = 71\%$
Test for overall effect: Z = 1.38 (P = 0.17)

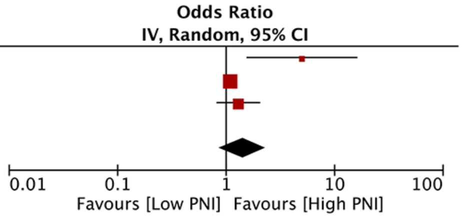


Figure 3. Meta-analysis of association between PNI and mortality after hip fractures.

with higher scores (OR: 3.61 95% CI: 1.70, 7.70 I^2=85% p=0.0009) (Figure 4). The results did not change during sensitivity analysis.

CONUT was used only by one study to assess malnutrition. The study of Kotera[21] classified patients as nourished and malnourished using the cut-off of 8. At six months, the number of patients with high CONUT (malnourished) had significantly higher mortality rates (23/198) in comparison with those with lower CONUT (10/392).

Discussion

Decreased food intake has been a predominant cause of malnutrition amongst the elderly. This is further exacerbated due to changes in smell and taste, hormonal alterations affecting gastrointestinal motility, and mood variations along with dementia, depression, and loneliness[24]. Post hip fractures, the malnourished group of elderly patients further enter a catabolic state resulting in reduced muscle mass and strength which may lead to adverse events. Indeed, this has been explored by several studies[25-27] in literature but with different indicators of malnutrition. Li et al[25] in 2019 found that serum albumin was an independent predictor of mortality after hip fractures. Nevertheless, serum albumin can be modified by baseline inflammatory state, comorbidities (liver diseases), and age itself. In individuals requiring surgery, there is both sterile and non-ster-

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Year
Koren-Hakim 2016	2.1277	0.549	17.3%	8.40 [2.86, 24.62]	2016
Miu 2017	0.9206	0.6217	15.7%	2.51 [0.74, 8.49]	2017
Helminen 2017	1.0818	0.2664	23.6%	2.95 [1.75, 4.97]	2017
Helminen 2019	2.4124	0.5518	17.2%	11.16 [3.78, 32.91]	2019
Thorling 2020	0.3853	0.1035	26.1%	1.47 [1.20, 1.80]	2020
Total (95% CI)			**100.0%**	**3.61 [1.70, 7.70]**	

Heterogeneity: $Tau^2 = 0.56$; $Chi^2 = 26.35$, df = 4 ($P < 0.0001$); $I^2 = 85\%$
Test for overall effect: Z = 3.33 (P = 0.0009)

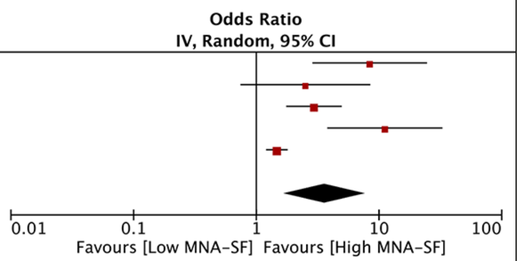


Figure 4. Meta-analysis of association between MNA-SF and mortality after hip fractures.

ile inflammation which causes reprioritization in liver leading to reduction in visceral protein synthesis bringing down the role of albumin as a malnutrition marker[26]. Another commonly used marker is BMI which has been shown to predict mortality after hip fractures[27]. However, the BMI classification does not take into consideration the extremities of age, comorbidities, and functional changes of the elderly[28]. Such limitations of singular measurements have left a vacuum in the nutritional screening of the elderly and prompted the development of multiple combination indices.

Of the various questionnaire-based tools, the MNA-SF is one the most validated and routinely used tools for nutritional assessment of the elderly. Developed in 2010, the MNA-SF consists of six questions combined with anthropometric measurements and mobility to classify the elderly as nourished or malnourished[29]. In our meta-analysis, it was noted that MNA-SF was an independent predictor of mortality after hip fracture surgery. Despite the high heterogeneity, the results were consistent across all included studies with no change in outcome on sensitivity analysis. Our results agree with the prior meta-analysis of three studies by Li et al[25] which too found MNA to be predictive of mortality after hip fracture. However, the previous review[25] combined both MNA and MNA-SF and used studies with overlapping data, thereby introducing bias in the analysis. By avoiding these errors and adding new studies, this review sets forth the latest and most accurate evidence on the role of MNA-SF for predicting mortality in hip fracture patients.

While MNA-SF is effective, simple, and easy to use, its subjective component is a major limitation. The PNI, GNRI, and CONUT are amongst the three most commonly used objective nutritional indices in recent years. The PNI combines albumin and lymphocyte count while CONUT is calculated by a combination of albumin, lymphocyte count, and cholesterol levels. GNRI is calculated by combining albumin and adjusted body weight. All three have been found to predict mortality in elderly patients with stroke[30], heart failure[31], aortic stenosis[32], and those undergoing spinal surgery[33]. However, to date their prognostic role in hip fractures has not been established. In our review, low GNRI was a significant predictor of mortality in elderly hip fracture patients. Similar to MNA-SF, the direction of the results was consistent across studies with stable results on sensitivity analysis. However, the limited data on PNI and CONUT was a significant limitation. The scarce data failed to establish the role of PNI in predicting mortality but the overall effect size being more than 1 does suggest that low PNI could lead to worse outcomes after hip fractures and the results need to be strengthened by further studies.

The clinical significance of these results lies in the fact that since malnutrition is predictive of mortality, nutritional interventions could help reduce adverse events in such patients. Indeed, there has been a spurt of studies[34,35] assessing the impact of nutritional supplementation in recent years. Takahashi et al[34] in a review have found that combined rehabilitation and nutritional therapy in elderly with hip fractures reduces mortality, postoperative complications and enhances grip strength. A Cochrane review[35] of 41 trials has suggested that oral micronutrients started just before or immediately after surgery can reduce complication rates, however, it failed to note any changes in mortality. Such contrasting results could be due to a large number of factors affecting mortality after hip fracture like gender, age, fracture type, comorbidity index, cognitive impairment, cardiac anomalies, and pre-fracture mobility[36]. Research[37] shows that outcomes after hip fracture can be improved by a more comprehensive approach of optimal nutrition, psychological support, and postoperative rehabilitation.

Limitations

One of the most important limitations of the review was the variable cut-offs noted with PNI and GNRI. Variation in cut-offs can change the number of individuals classified as malnourished leading to bias. However, this limitation is common amongst meta-analyses[38-41] on such objective indices as different authors use different cut-offs based on the studied population. This, along with differences in baseline comorbidities, fracture types, surgical intervention, post-operative rehabilitation, and follow-up period may have contributed to high heterogeneity in the meta-analysis. Other limitations of the review are the low number of studies in the meta-analysis and the observational nature of data which could introduce bias in the results. The scarce data also precluded subgroup analyses based on different variables. Furthermore, not all studies were of high quality based on NOS score, with most studies having moderate risk of bias and five having high risk of bias. Lastly, several confounders can affect mortality and many known and unknown confounders would not have been adjusted by the included studies resulting in biased results.

The strength of the review includes a comprehensive assessment of four different nutritional markers in a single study. Ours is the first study to collate data on PNI, CONUT, and GNRI for hip fractures. A detailed literature search was conducted along with gray literature to include maximum studies in the meta-analysis.

Conclusions

Our results indicate that MNA-SF and GNRI can predict mortality in elderly patients undergoing surgery for hip fractures. Data is scarce on PNI and CONUT to draw strong conclusions. Variation in cut-offs and follow-up period are important limitations which need to be addressed by future studies.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contribution

NL conceived and designed the study, JJ, YZ and XZ collected data and performed data analysis. NL wrote the draft of this manuscript. LL edited the manuscript.

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