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ORIGINAL RESEARCH

ISCHEMIC HEART DISEASE

Cardiovascular Outcomes in Acute Coronary Syndrome and Malnutrition

A Meta-Analysis of Nutritional Assessment Tools

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ABSTRACT

BACKGROUND There is emerging evidence that malnutrition is associated with poor prognosis among patients with acute coronary syndrome (ACS).

OBJECTIVES This study seeks to elucidate the prognostic impact of malnutrition in patients with ACS and provide a quantitative review of most commonly used nutritional assessment tools.

METHODS Medline and Embase were searched for studies reporting outcomes in patients with malnutrition and ACS. Nutritional screening tools of interest included the Prognostic Nutrition Index, Geriatric Nutritional Risk Index, and Controlling Nutritional Status. A comparative meta-analysis was used to estimate the risk of all-cause mortality and cardiovascular events based on the presence of malnutrition and stratified according to ACS type, ACS intervention, ethnicity, and income.

RESULTS Thirty studies comprising 37,303 patients with ACS were included, of whom 33.5% had malnutrition. In the population with malnutrition, the pooled mortality rate was 20.59% (95% CI: 14.95%-27.67%). Malnutrition was significantly associated with all-cause mortality risk after adjusting for confounders including age and left ventricular ejection fraction (adjusted HR: 2.66, 95% CI: 1.78-3.96, $P = 0.004$). There was excess mortality in the group with malnutrition regardless of ACS type ($P = 0.132$), ethnicity ($P = 0.245$), and income status ($P = 0.058$). Subgroup analysis demonstrated no statistically significant difference in mortality risk between individuals with and without malnutrition ($P = 0.499$) when using Controlling Nutritional Status (OR: 7.80, 95% CI: 2.17-28.07, $P = 0.011$), Geriatric Nutritional Risk Index (OR: 4.30, 95% CI: 2.78-6.66, $P < 0.001$), and Prognostic Nutrition Index (OR: 4.67, 95% CI: 2.38-9.17, $P = 0.023$).

CONCLUSIONS Malnutrition was significantly associated with all-cause mortality risk following ACS, regardless of ACS type, ethnicity, and income status, underscoring the importance of screening and interventional strategies for patients with malnutrition. (JACC Adv 2023;2:100635) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

CABG = coronary artery bypass graft

CONUT = Controlling Nutritional Status

CVD = cardiovascular disease

GNRI = Geriatric Nutritional Risk Index

MACE = major adverse cardiovascular events

NSTE-ACS = non ST-segment elevation acute coronary syndrome

PNI = Prognostic Nutrition Index

STEMI = ST-segment elevation myocardial infarction

Mortality following acute coronary syndrome (ACS) remains high, and life-threatening coronary artery disease is often predisposed by cardiovascular disease (CVD) risk factors such as type 2 diabetes mellitus, hypertension, and dyslipidemia.[1] Emerging evidence has shown a possible J-curve association between nutrition and CVD, and the identification of this modifiable risk factor may potentially allow for better risk stratification of patients with ACS.[1,2] Various nutritional assessment tools used to categorize malnutrition, such as the Prognostic Nutrition Index (PNI), Geriatric Nutritional Risk Index (GNRI), and Controlling Nutritional Status (CONUT), have been developed and demonstrated to possess prognostic utility in the prognostication of ACS.[3-5] These past studies have postulated that hypoalbuminemia is correlated with a proinflammatory environment, although the exact cause-and-effect mechanism between them is unclear.[3,4] Moreover, the immunocompromised state indicated by lymphocytopenia in these patients may further contribute to the poor prognosis.[3,5]

With 10% or more of patients with ACS suffering from malnutrition,[6] early identification and management of malnutrition have the potential to improve outcomes for this vulnerable group of patients. However, while malnutrition is a risk factor that can be readily intervened,[7] it is often overlooked in clinical practice.[8] This is in part due to the lack of a standardized definition or method to assess nutritional status and the numerous different types of tools available.[9,10] There is limited evidence in the current literature suggesting which tool is superior prognostically, a relevant factor that may help clinicians in the selection of tool to use.

While studies have examined malnutrition in CVD, few have focused specifically on patients with ACS.[11-14] Furthermore, current meta-analyses addressing the prognostic impact of malnutrition on patients with ACS often examine individual nutritional indices but do not compare different widely used nutritional assessment tools.[8,9] Hence, this paper seeks to elucidate the prognostic impact of malnutrition in patients with ACS by examining the outcomes of all-cause mortality, major adverse cardiovascular outcomes, and other cardiovascular outcomes, as well as medication usage across the total follow-up duration reported in the studies. Moreover, we aim to comprehensively consolidate and compare the utility of the most commonly used nutritional assessment tools.

METHODS

SEARCH STRATEGY. This study was conducted with reference to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[15] and was registered with PROSPERO (CRD42022334482). Ethical approval was not required because this meta-analysis utilized data from published studies. A search was conducted on Medline and Embase to identify literature published from inception to May 18, 2022, relating to the outcomes of patients with ACS and

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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malnutrition compared to patients without malnutrition. Keywords included in the search strategy were "malnutrition", "nutritional assessment", and "acute coronary syndrome" (Supplemental Appendix). References were imported into Endnote (Version 20, Clarivate) for removal of duplicates.

STUDY SELECTION AND DATA EXTRACTION. Title and abstract sieve, and full text review were conducted independently by 2 authors (A.L.R.X. and E.N.Z.X.). Disputes were resolved by a senior author (N.C.W.S.). The inclusion criteria were: 1) cohort studies examining the outcomes of adult (aged 18 and above) participants; 2) populations with ACS; and 3) utilized a nutritional index to classify patients as with or without malnutrition. A description of the various nutritional indices can be found in Supplemental Table 1 inclusive of PNI,[16] GNRI,[17] CONUT,[18] Nutrition Risk Screening-2002,[19] Malnutrition Screening Tool,[20] Mini Nutritional Assessment,[21] Mini-Nutritional Assessment-Short Form,[22] and Triglyceride, Total Cholesterol and Body Weight Index.[23] ACS was defined in accordance with the clinical practice guidelines, inclusive of ST-segment elevation myocardial infarction (STEMI), and non-ST-segment elevation ACS (NSTE-ACS).[24] Meta-analyses, systematic reviews, case reports, position papers, commentaries, conference abstracts, and randomized controlled trials were excluded. Studies were also excluded if they involved special patient groups such as cancer or pediatric patients. For studies that reported on the same patient pool in overlapping time periods, we included the most comprehensive article.

Data was extracted independently by 3 authors (A.L.R.X., M.W., and E.N.Z.X.). The extracted information included study characteristics and patient demographics. In addition, we extracted survival and cardiovascular outcomes of interest, namely all-cause mortality, in-hospital mortality, cardiac mortality, major adverse cardiovascular events (MACE), cerebrovascular accidents, and coronary revascularization. In most articles, MACE was defined as the composite of all-cause mortality, myocardial infarction, revascularizations, and ischemic stroke, while coronary revascularization included percutaneous coronary intervention and coronary artery bypass graft (CABG). Transformation of values from median and interquartile range to mean and standard deviation were carried out when they were not stated.[25] The primary outcome was all-cause mortality. Secondary outcomes included in-hospital mortality, cardiac mortality, MACE, cerebrovascular accidents, and coronary revascularization. Unless otherwise stated, the follow-up time period used for analysis was the entire follow-up time period reported in the various studies.

STATISTICAL ANALYSIS AND QUALITY ASSESSMENT. Statistical analysis was conducted using RStudio (Version 4.1.0). For the analysis of variables reported as proportions, a single-arm meta-analysis of proportions was conducted using a generalized linear mixed model with Clopper-Pearson intervals in order to stabilize the variance using the *metaprop* function.[26-28] To estimate the effects of malnutrition on patient outcomes, the OR was determined using a generalized linear model using the *metabin* function.[29,30] Next, the inverse variance method was used to conduct a meta-analysis of means for the analysis of data reported as continuous variables using the *metamean* function. Cochrane Review Manager (Version 5.4.1) was used to pool HRs using the inverse variance method.[31] For this analysis, we pooled the unadjusted HR and adjusted HR of all-cause mortality separately. Where studies reported more than one set of adjusted HR, the results of the most comprehensive analysis that included the most covariates were extracted. The random effects model was utilized since the pooled studies differed in trial characteristics such as inclusion and exclusion criteria and study duration.[32] Hartung-Knapp adjustments were used to adjust for confidence intervals.[33] Results of the statistical analysis were considered significant if they had a value of $P \leq 0.05$. Small, moderate, and large amounts of heterogeneity were defined with I^2 cutoffs of 25%, 50%, and 75%, respectively.[34] Publication bias was assessed via a funnel plot.

Subgroup analysis was conducted to analyze the difference in outcomes by nutritional assessment tools (CONUT, GNRI, PNI, others), mean age (<65 years, ≥65 years), ethnicity (predominantly Asian, predominantly White), duration of follow-up (<2 years, ≥2 years), type of ACS (ACS, STEMI, NSTE-ACS), and income group (high, upper middle). Subgroup analysis was done with the *byvar* argument in Rstudio, and *P* values from the test of subgroup difference were reported. In the respective subgroups, the results of the statistical analysis comparing patients with malnutrition to patients without malnutrition were also reported in terms of OR and its corresponding *P* value. We followed the World Bank classification of countries for income group, and Asian ethnicity was defined as individuals from East Asia, Central Asia, South Asia, and Middle East heritage.[35] In addition, we also conducted a separate analysis involving studies that followed the more widely adopted guidelines for malnutrition for the primary outcome of all-cause mortality. The

cutoffs used were CONUT ≥2, GNRI <98, and NRS-2002 ≥3 (Supplemental Table 1).

RISK OF BIAS ASSESSMENT. Risk of bias assessment was carried out using the Newcastle-Ottawa Scale by 3 independent authors (A.L.R.X., M.W., and E.N.Z.X.). In the event of disagreements, a fourth independent author (Y.H.C.) was recruited to resolve disputes. The 3 domains of bias assessed are: selection of study groups; comparability of these groups; and ascertainment of exposure or outcome of interest.[36] The maximum possible score is 9.

RESULTS

SUMMARY OF INCLUDED ARTICLES. The search yielded 3,786 results, of which 776 duplicates were removed. A total of 2,776 studies were excluded after title and abstract sieve, with 234 studies selected for full text review. A final total of 30 studies were included in this meta-analysis (**Figure 1**). Of these 30 studies, 20 were from Asia, 9 were from Europe, and 1 was from South America. A total of 37,303 individuals were included, of whom 12,494 (33.5%) had malnutrition and 24,621 did not. The mean ages of the patients with and without malnutrition were 72 years and 65 years, respectively, and they were predominantly males (67.1% and 74.5%, respectively). The mean body mass index of the patients with and without malnutrition was 24.4 kg/m^2 and 26.7 kg/m^2, respectively, and the proportion of smokers was 36.1% and 43.8%, respectively. A summary of the included articles can be found in Supplemental Table 2.

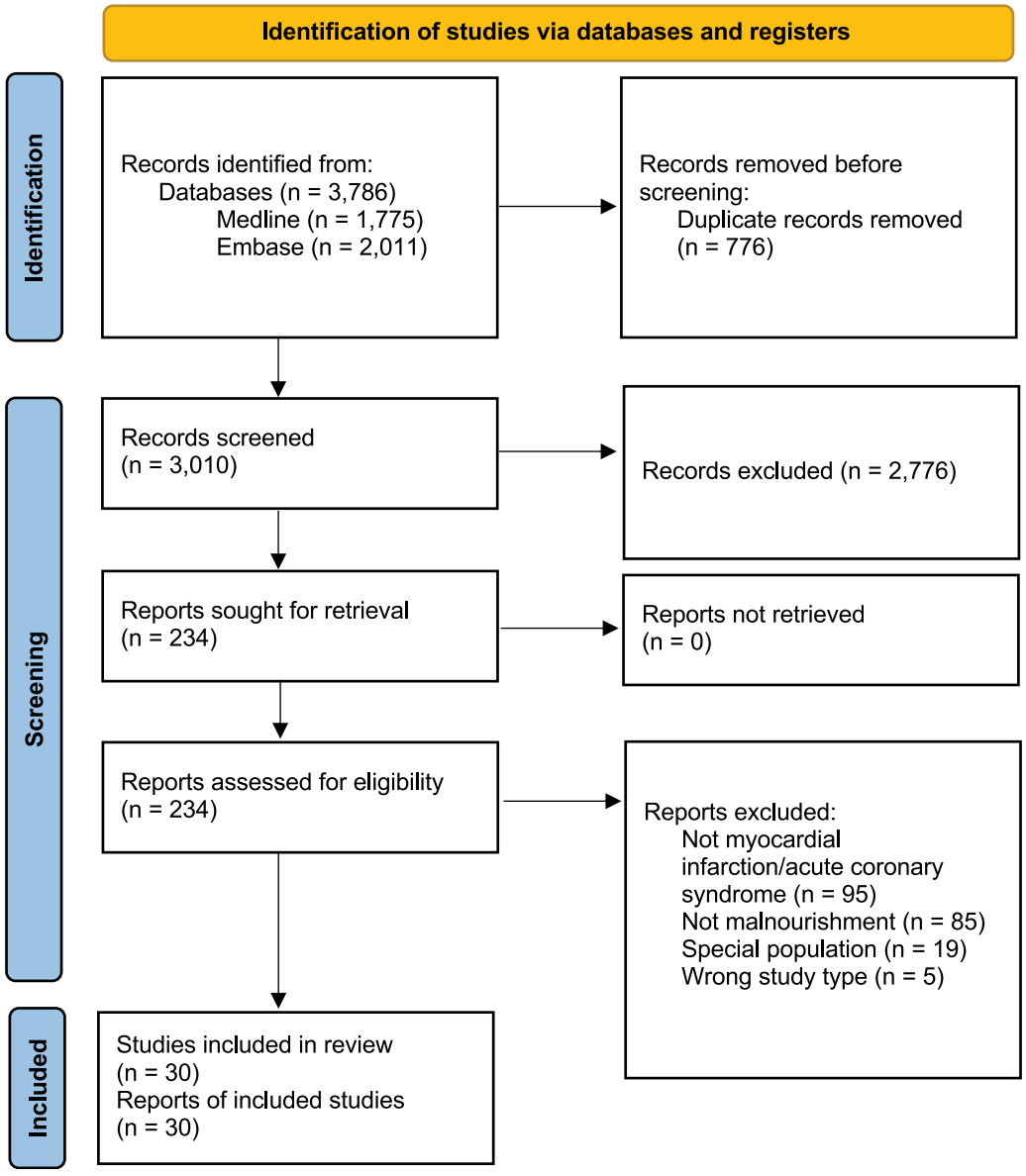
BASELINE CHARACTERISTICS. The comparison of baseline characteristics can be found in Supplemental Table 3. The prevalence of dyslipidemia was significantly higher in the group without malnutrition (39.6%, 95% CI: 25.6%-55.6%) compared to the group with malnutrition (33.8%, 95% CI: 19.6%-51.3%, $P = 0.017$). The prevalence of hypertension and type 2 diabetes mellitus was similar between the 2 groups. When comparing laboratory markers of nutrition, the group with malnutrition had significantly lower serum albumin levels and lymphocyte counts. They also had significantly lower levels of low-density lipoprotein, total cholesterol, and triglyceride.

PRIMARY OUTCOMES. There were 25 studies comprising 34,593 patients reporting data on all-cause mortality with a mean follow-up duration of 33 months (range: 9-43 months) (**Table 1**). The temporal trend of all-cause mortality is presented in Supplemental Table 4 and **Figure 2**. In the group with malnutrition, the pooled mortality rate was 20.59% (95% CI: 14.95%-27.67%), increasing from 3.22% (95% CI: 1.33%-7.59%) at 30 days, 12.48% (95% CI: 7.37%-20.38%) at 1 year, 16.49% (95% CI: 6.65%-35.36%) at 2 years, to 37.92% (95% CI: 25.06%-52.74%) at 5 years. In contrast, the pooled mortality rate was lower in the group without malnutrition (5.41%, 95% CI: 3.44%-8.39%), with smaller increases in mortality rates over time: 1.02% (95% CI: 0.47%-2.24%) at 30 days, 2.44% (95% CI: 1.25%-4.70%) at 1 year, 2.32% (95% CI: 0.79%-6.58%) at 2 years, and 12.38% (95% CI: 8.40%-17.87%) at 5 years. Patients with malnutrition following ACS had a higher risk of all-cause mortality compared to their counterparts (unadjusted HR: 4.36, 95% CI: 3.06-6.22, $P < 0.001$). Malnutrition was significantly associated with all-cause mortality risk even after adjusting for possible confounders such as age and left ventricular ejection fraction (adjusted HR: 2.66, 95% CI: 1.78-3.96, $P = 0.004$) (Supplemental Table 5). The model covariates used by the individual studies for analysis are reported in Supplemental Table 2. Funnel plot analysis showed no publication bias (Supplemental Figure 1).

Baseline demographics. There was no difference in all-cause mortality ($P = 0.245$) between Asian (OR: 4.87, 95% CI: 3.44-6.91, $P < 0.001$) and White (OR: 3.37, 95% CI: 1.68-6.74, $P = 0.006$) ethnicities. Similarly, the upper-middle (5.84, 95% CI: 3.93-8.67, $P < 0.001$) and high (3.50, 95% CI: 2.25-5.43) income groups had similar mortality risks ($P = 0.058$). In the subgroup analysis based on age cutoff of 65 years old, patients with malnutrition who were older did not have higher mortality risk (OR: 6.93, 95% CI: 3.39-14.15, $P < 0.001$) compared to those who were younger (OR: 3.67, 95% CI: 2.69-5.01, $P < 0.001$). However, the group with malnutrition had higher mortality rates in both the STEMI (OR: 7.21, 95% CI: 3.05-17.04, $P = 0.002$) and NSTE-ACS subgroups (OR: 4.99, 95% CI: 2.38-10.46, $P = 0.006$).

Type of nutritional score. Subgroup analysis based on nutritional assessment tools demonstrated no difference in their prognosticating ability of all-cause mortality between patients with and without malnutrition ($P = 0.499$) when using CONUT (OR: 7.80, 95% CI: 2.17-28.07, $P = 0.011$), GNRI (OR: 4.30, 95% CI: 2.78-6.66, $P < 0.001$), and PNI (OR: 4.67, 95% CI: 2.38-9.17, $P = 0.023$). When comparing across studies that adhered to the more widely used nutritional tool cutoffs (as defined in Supplemental Table 1), higher odds of mortality ($P = 0.018$) were noted for CONUT (OR: 3.78, 95% CI: 2.97-4.82, $P < 0.001$), while statistical significance was not achieved using GNRI

FIGURE 1 PRISMA Flow Diagram



A total of 3,786 articles were identified from Medline and Embase, of which 30 articles were included. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

(OR: 6.90, 95% CI: 0.44-107.95, $P = 0.071$) (Supplemental Table 6). The forest plots of all-cause mortality and subgroup analysis can be found in **Figure 3**.

SECONDARY OUTCOMES. The summary of secondary outcomes is presented in **Table 1** and **Figure 4**. Compared to the group without malnutrition, the group with malnutrition had a higher risk of MACE following ACS (OR: 2.74, 95% CI: 2.14-3.51, $P < 0.001$, mean follow-up duration: 39 months, range: 20-43 months), in-hospital mortality (OR: 5.83, 95% CI: 3.29-10.33, $P < 0.001$, mean follow-up duration: 20 months, range: 12-33 months), cardiac mortality (OR: 3.74, 95% CI: 1.77-7.88, $P = 0.005$, mean follow-up duration: 24 months, range: 11-32 months), and cerebrovascular accidents (OR: 3.42, 95% CI: 1.98-5.93, $P = 0.003$, mean follow-up duration: 31 months, range: 20-39 months). There was no difference in

TABLE 1 Prognostic Outcomes Following Acute Coronary Syndrome Across the Entire Follow-Up Duration, Pooled and With Stratification by Subgroups

		With Malnutrition			Without Malnutrition			Comparison of Patients With Malnutrition Against Without Malnutrition		
	Studies	Proportion (95% CI)	I^2	*P* Value	Proportion (95% CI)	I^2	*P* Value	OR (95% CI)	I^2	*P* Value
All-cause mortality										
Overall	25	20.59% (14.95%-27.67%)	96.0%		5.41% (3.44%-8.39%)	97.0%		4.51 (3.33-6.12)	87.0%	**<0.001**
Nutritional assessment tool				0.717			0.181			0.499
CONUT	5	15.14% (5.43%-35.66%)	96.4%		2.18% (0.52%-8.61%)	94.5%		7.80 (2.17-28.07)	87.3%	**0.011**
GNRI	10	21.33% (10.47%-38.61%)	96.6%		5.90% (2.34%-8.61%)	95.8%		4.30 (2.78-6.66)	82.2%	**<0.001**
PNI	5	24.38% (11.72%-43.90%)	97.0%		6.75% (3.11%-14.02%)	97.9%		4.67 (2.38-9.17)	86.1%	**0.023**
Others	5	21.66% (13.65%-32.58%)	89.2%		7.79% (2.97%-18.94%)	98.4%		3.29 (1.31-8.31)	91.6%	**0.003**
Mean age, y				0.166			**0.002**			0.052
<65	7	16.38% (7.51%-32.11%)	95.8%		2.89% (1.41%-5.86%)	91.0%		6.93 (3.39-14.15)	83.8%	**<0.001**
≥65	17	25.28% (19.39%-32.11%)	94.8%		8.37% (5.58%-12.37%)	96.4%		3.67 (2.69-5.01)	83.5%	**<0.001**
Type of ACS				0.293			0.099			0.132
ACS	15	22.82% (16.63%-30.46%)	96.0%		7.47% (4.42%-12.36%)	97.4%		3.61 (2.58-5.05)	85.7%	**<0.001**
STEMI	6	23.51% (8.86%-49.30%)	95.7%		4.34% (1.58%-11.33%)	93.2%		7.21 (3.05-17.04)	84.8%	**0.002**
NSTE-ACS	4	10.70% (2.00%-41.24%)	96.0%		2.12% (0.32%-12.93%)	82.9%		4.99 (2.38-10.46)	29.6%	**0.006**
Duration of follow-up				0.986			0.742			0.560
2 y or less	12	20.40% (16.19%-25.37%)	85.5%		4.96% (3.04%-7.97%)	97.4%		4.93 (2.91-8.37)	87.8%	**<0.001**
More than 2 y	13	20.50% (10.88%-35.28%)	97.4%		5.73% (2.47%-12.72%)	96.5%		4.16 (2.88-8.37)	86.9%	**<0.001**
Ethnicity				**0.036**			**0.008**			0.245
Predominantly Asian[a]	19	18.19% (12.04%-26.55%)	96.3%		3.23% (2.46%-7.16%)	93.1%		5.03 (3.54-7.16)	80.5%	**<0.001**
Predominantly White	6	29.51% (20.31%-40.75%)	96.2%		11.10% (5.63%-20.72%)	97.0%		3.37 (1.68-6.74)	92.6%	**0.006**
Prospective/retrospective				0.158			0.286			0.636
Prospective	8	15.89% (10.22%-23.86%)	90.5%		4.11% (2.19%-7.60%)	87.9%		4.10 (2.92-5.75)	45.4%	**<0.001**
Retrospective	17	23.11% (15.03%-33.82%)	96.0%		6.20% (3.40%-11.02%)	97.1%		4.62 (2.99-7.13)	90.7%	**<0.001**
Income group				0.317			**0.043**			0.058
High	12	23.79% (17.33%-31.74%)	95.7%		8.21% (4.61%-14.21%)	97.0%		3.50 (2.25-5.43)	87.6%	**<0.001**
Upper middle	13	17.81% (9.80%-30.18%)	96.3%		3.71% (1.94%-7.00%)	92.3%		5.84 (3.93-8.67)	78.1%	**<0.001**
Other outcomes										
Cardiac mortality	7	11.37% (4.35%-26.59%)	95.9%		3.47% (1.79%-6.64%)	87.0%		3.74 (1.77-7.88)	78.6%	**0.005**
In-hospital mortality	8	16.40% (10.85%-24.02%)	95.8%		3.24% (2.09%-4.99%)	84.1%		5.83 (3.29-10.33)	89.6%	**<0.001**
MACE	11	27.48% (19.01%-37.96%)	97.8%		11.89% (7.86%-17.60%)	98.6%		2.74 (2.14-3.51)	86.6%	**<0.001**
Cerebrovascular accident	5	3.43% (1.15%-9.72%)	81.9%		1.47% (0.64%-3.31%)	70.5%		3.42 (1.98-5.93)	0.0%	**0.034**
Coronary revascularization	8	16.35% (3.86%-48.74%)	98.8%		18.04% (3.87%-54.60%)	99.4%		0.98 (0.61-1.57)	86.1%	0.933
Medications										
Aspirin	9	92.36% (73.69%-98.12%)	97.7%		93.78% (75.52%-98.66%)	99.2%		0.92 (0.70-1.21)	33.6%	0.510
Beta-blockers	12	70.96% (50.26%-85.52%)	97.3%		74.77% (55.47%-87.58%)	98.8%		0.78 (0.67-0.90)	45.4%	**0.004**
ARB	12	68.68% (49.99%-82.79%)	98.4%		69.79% (50.22%-84.10%)	98.8%		0.99 (0.83-1.17)	69.2%	0.853
Statins	13	89.38% (71.69%-96.55%)	97.2%		94.00% (74.28%-98.84%)	99.3%		0.71 (0.41-1.23)	91.5%	0.200

Bold values indicate *P* value of <0.05 and it is taken as statistical significance. [a]Predominantly Asian included all Asian ethnicities.

ACS = acute coronary syndrome; ARB = angiotensin receptor blocker; CABG = coronary artery bypass graft; CONUT = controlling nutritional status; GNRI = Geriatric Nutritional Risk Index; MACE = major adverse cardiovascular outcomes; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; NSTEMI = non-ST-segment elevation myocardial infarction; PNI = Prognostic Nutrition Index; STEMI = ST-segment elevation myocardial infarction.

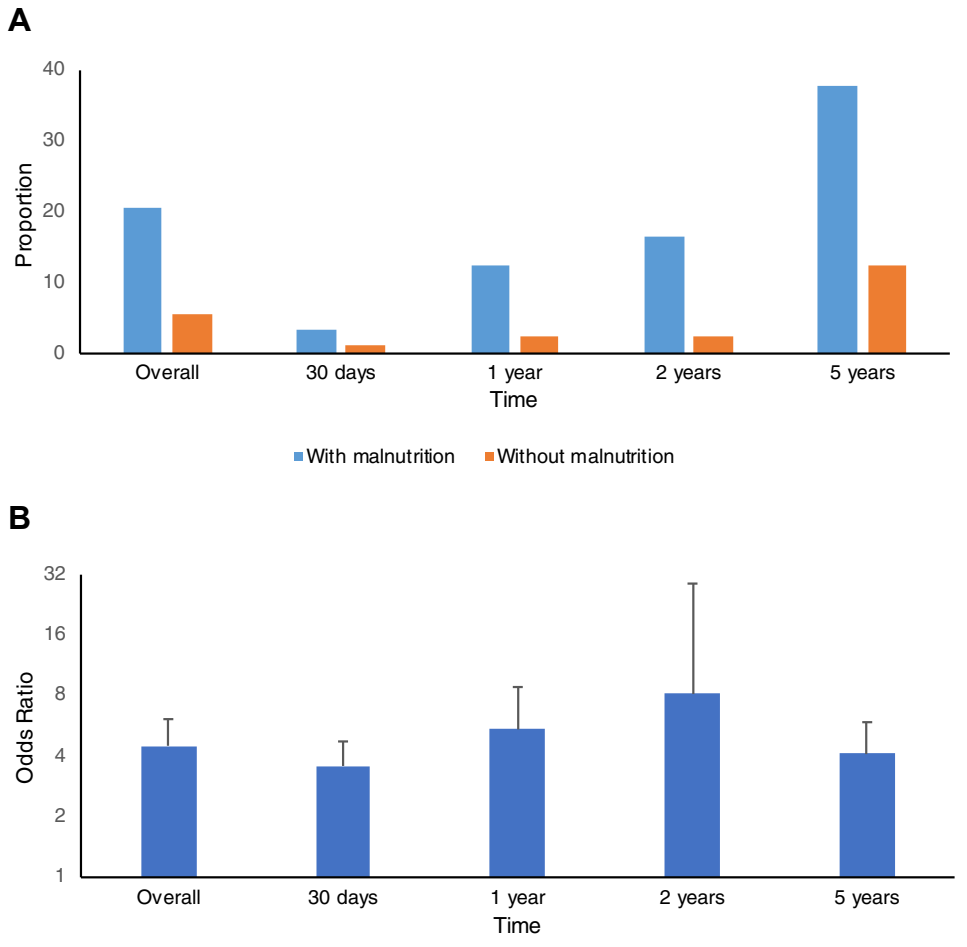
coronary revascularization rates between the 2 groups (mean follow-up duration: 23 months, range: 9-39 months).

GUIDELINE-DIRECTED MEDICAL THERAPY. In terms of guideline-directed medical therapy following ACS, the group with malnutrition had a lower use of beta-blockers (OR: 0.78, 95% CI: 0.67-0.90, $P = 0.004$) compared to the group without malnutrition, but there were no differences in the use of aspirin, angiotensin receptor blockers, and statins between the 2 groups (Table 1).

DISCUSSION

In this meta-analysis, we showed that malnutrition was significantly associated with all-cause mortality risk in patients with ACS, even after adjusting for important confounders.[7,37] Two in 5 patients do not

FIGURE 2 Bar Plot of All-Cause Mortality, Stratified by Follow-Up Duration

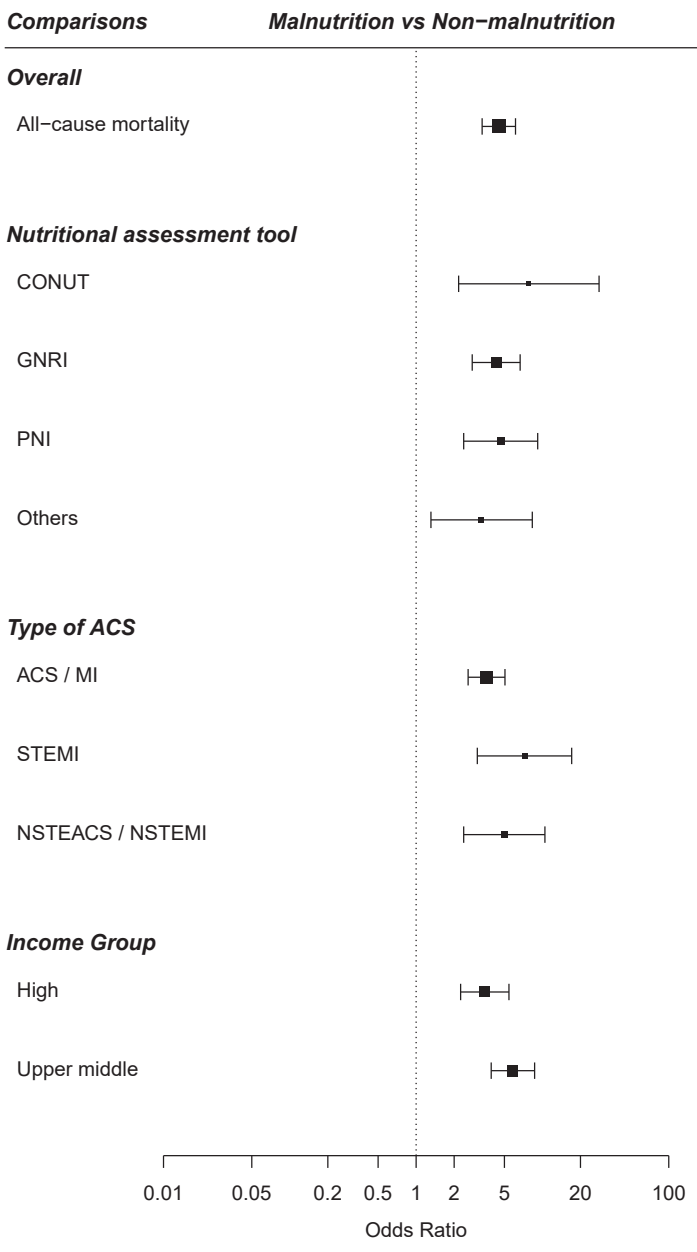


(A) Proportion, (B) odds ratio. Regardless of the follow-up duration (mean: 33 months, range: 9-43 months), there was increased odds of all-cause mortality in patients with malnutrition.

survive beyond 5 years after the index ACS event, emphasizing the importance of addressing poor nutritional status in the post-ACS care bundle. Moreover, with the various nutritional tools available, it is important to harmonize the diagnosis of malnutrition in patients with CVD. Importantly, this study highlighted similar prognostic capabilities across the various tools, which may suggest the consideration of other factors, such as the ease and availability of the prognostic biomarkers, when deciding the preferred tools to be adopted for use in clinical practice (**Central Illustration**).

Compared to the group without malnutrition, the patients with malnutrition had significantly lower cholesterol levels, body mass index, and smoking prevalence,[38] but they had excess mortality post-ACS throughout the various time periods, regardless of ACS type, ethnicity, and income status. Moreover, individuals with malnutrition and ACS had an increased risk of other complications including stroke and MACE. Given the anti-inflammatory and anti-oxidative properties of serum albumin,[39] studies have postulated that the lowered levels of albumin in patients with malnutrition[9,40] may exacerbate the inflammatory process,[41] resulting in higher atherosclerotic burden[42] and predisposing to various comorbidities.[43-45] In line with the recommendations of present clinical practice guidelines, nutrition is an important modifiable risk factor not to be neglected in clinical settings, though scientific evidence in this patient population is lacking,[46] and this calls for greater awareness among clinicians in the evaluation of nutritional status in all patients with ACS.[47] Indeed, there are emerging interests in the

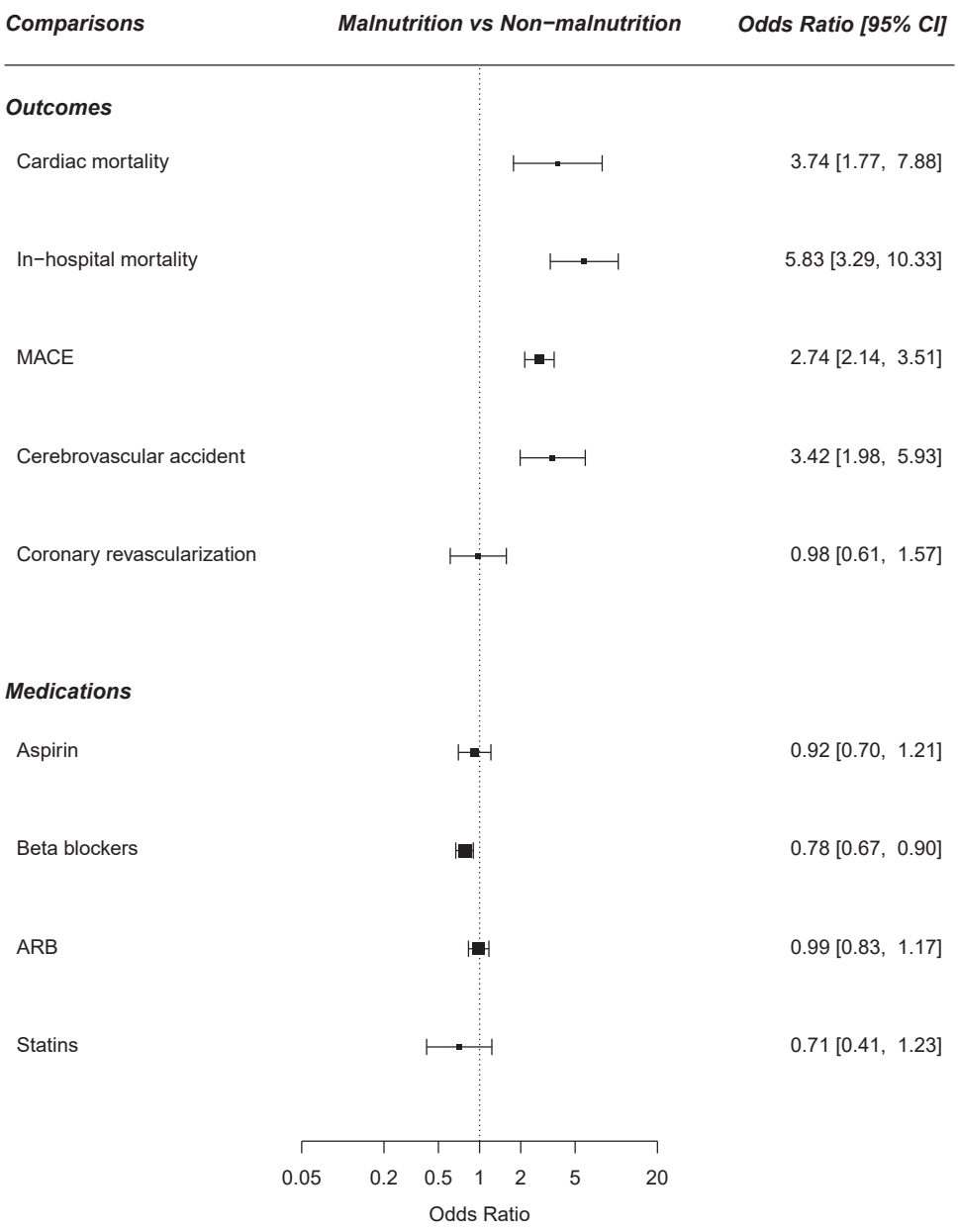
FIGURE 3 Summary Plot of All-Cause Mortality, With Stratification by Selected Subgroups



All-cause mortality was higher in patients with malnutrition (mean follow-up duration: 33 months, range: 9-43 months), with no significant difference when comparing the various subgroups.

applicability of nutritional assessment tools used in patients with CVD[48] beyond its traditional utility in the geriatric or cancer cohorts.[49,50] The importance of malnutrition screening in patients with ACS in the early identification and nutritional management of these individuals should not be understated and aggressively screened for. Exercise training has been highlighted as a crucial interventional strategy in patients with malnutrition, which has a net positive effect on muscle function and renutrition.[51] However, there are barriers to the implementation of dietary and exercise interventions in various patient groups.[52] Hence, the multidisciplinary approach involving dietitians and other allied healthcare workers remains paramount in achieving optimal nutritional status in the ACS care bundle.[53] Beyond

FIGURE 4 Summary Plot of Outcomes and Medications

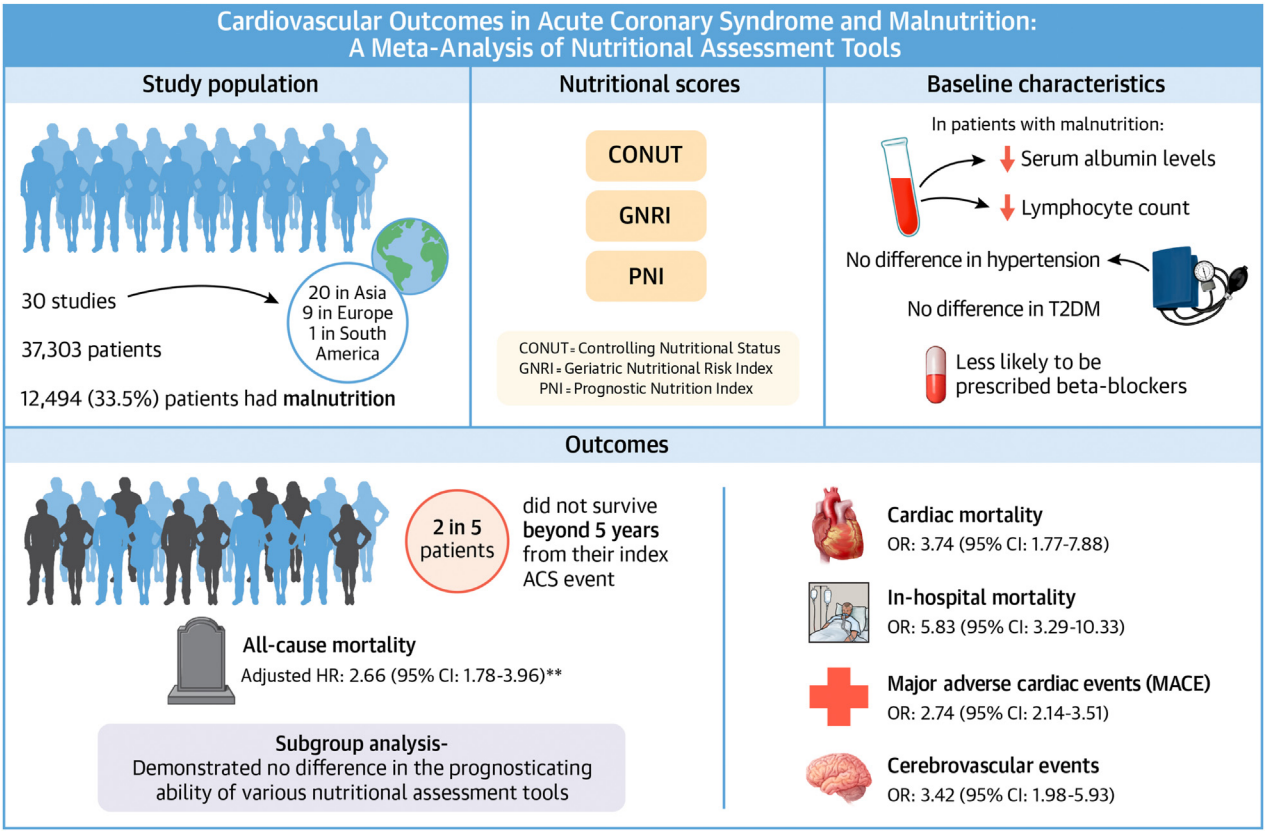


Patients with malnutrition had higher rates of cardiovascular outcomes and a lower rate of beta-blocker usage when comparing against the entire follow-up duration.

the need for global efforts for the implementation of malnutrition-based patient stratification, it is pertinent to investigate the most appropriate and efficacious nutritional intervention to improve patient outcomes.

Malnutrition and obesity are not mutually exclusive and may coexist.[54] Complicating the matter is the obesity paradox, in which the presence of obesity has been suggested to confer a favorable prognosis in patients with CVDs.[55] A greater physiological reserve has been proposed as a plausible reason,[55] but this may not exist in patients with malnutrition. Future research should ascertain the impact of the double burden of malnutrition and obesity in patients with CVDs. Next, our study notes the fewer prescriptions of beta-blockers observed in the group with

CENTRAL ILLUSTRATION **Our Study Included 37,303 Patients, of Which 33.5% Had Malnutrition**



Lai ARX., et al. JACC Adv. 2023;2(8):100635.

The adjusted hazard ratio for the primary outcome of all-cause mortality was 2.66 when comparing against the entire follow-up duration, and there was no significant difference in the prognostic capability of nutritional screening tools. **Adjusted for age, sex, type 2 diabetes mellitus, hypertension and baseline cardiovascular diseases.

malnutrition, which may have been eschewed due to pre-existing hypotension, chronic obstructive pulmonary disease, or frailty in patients with malnutrition.[56] Aggressive implementation of guideline-directed medical and nutritional therapy in patients needs to be the focus in order to improve their chances of morbidity-free survival.

Despite the various nutritional assessment tools available, with the most used scores being CONUT, GNRI, and PNI, there is currently no guidance on the suitability of these scores in the context of ACS. Preceding any consensus on the determination of the ideal nutritional assessment tool in the cohort with ACS, the comparison of the commonly used nutritional tools in terms of their prognostic utility in the prognosis of patients with ACS will be the next important step. With the present study's large sample size, we were not able to detect any significant differences across the various scores used when examining the odds of all-cause mortality in the groups with malnutrition compared to those without malnutrition. This may be due to overlaps in the methods of calculation among the various tools, where most studies have included measures relating to albumin and body weight as markers of malnutrition. Clinicians need to be cognizant of the practicality of administering these tools in the acute setting, with the advantage of CONUT, GNRI, PNI, and Triglyceride, Total Cholesterol and Body Weight Index using readily available laboratory tests, while others such as Mini Nutritional Assessment and Malnutrition Universal Screening Tool[57] require more holistic evaluation with the use of comprehensive questionnaires. With the practical challenges surrounding the

qualitative assessment of nutritional status, especially in the setting of ACS, there also remains a lack of research data using these approaches, and hence our study was unable to include these tools in the analysis. Moreover, only 8 out of the 25 included studies analyzed adhered to the widely used malnutrition cutoffs, while the others had their own definitions. Though the possibility of reporting bias from the adjustment of thresholds cannot be completely ruled out,[58] the heterogeneity in the cutoffs used may be attempts in contextualizing the measures to the specific population. Similar to how the definition of overweight was adjusted for Asian populations,[59] adjustment of cutoff values for baseline demographics may be necessary in the context of malnutrition. This calls for the concerted effort in harmonizing the definition of malnutrition in CVD and establishing the appropriate nutritional assessment tools and their respective tool-specific cutoffs.

STRENGTHS AND LIMITATIONS. This study provides a comprehensive consolidation of the prognostic capability of commonly used nutritional assessment tools in populations with ACS and malnutrition, providing important comparisons by the type of tool as well as survival trends across various subgroups based on epidemiological or clinical factors. However, the study has its limitations. Firstly, there was a paucity of data on baseline demographics such as B-type natriuretic peptide and the NYHA functional class, limiting our ability to depict the health status of patients. Similarly, we were unable to conduct participant-level subgroup analyses based on important variables such as sex. Nonetheless, the significantly higher adjusted hazard ratio of all-cause mortality highlights that malnutrition is correlated with poorer prognosis in patients with ACS. Next, nutritional status may change over time. However, examining temporal trends in the degree of malnutrition was not possible in this study, given the paucity of granular data such as nutritional supplementation. In addition, due to the lack of data, the paper was unable to evaluate nutritional assessment tools such as the Malnutrition Universal Screening Tool, thus limiting the applicability of the results to clinical settings that adopt these tools. Nevertheless, the paper was able to capture most of the commonly used tools such as GNRI, CONUT, and PNI. However, the inclusion of various tools in our analysis increases heterogeneity. Nonetheless, most of the tools seek to evaluate similar parameters in patients, and subgroup analysis based on the type of nutritional assessment tools showed similar prognostic efficacy. Lastly, this paper was unable to establish the potential correlation between sarcopenia, specific fat depots, and malnutrition due to the lack of data reported in the included articles.

CONCLUSIONS

Malnutrition was significantly associated with all-cause mortality risk following ACS, with a 2.6-fold higher risk of mortality compared to the patients without malnutrition. Excess mortality was observed in patients with malnutrition regardless of ACS type, ethnicity, and income status, thus underscoring the importance of malnutrition screening for early identification. Although nutritional screening tools such as GNRI, CONUT, and PNI are readily available with similar prognostic capabilities, clinical interpretation still needs to be tailored in the context of the tool used. Concerted efforts in the harmonization of the screening tools and definition of malnutrition in patients with CVD will be the next important step.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE: Malnutrition was significantly associated with all-cause mortality risk following ACS, and commonly used nutritional screening tools share similar prognostic capabilities. Aggressive implementation of guideline-directed nutritional therapy is needed.

TRANSLATIONAL OUTLOOK: Concerted effort in harmonizing the definition of malnutrition in ACS is the next important step.

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KEY WORDS **acute coronary syndrome, coronary artery disease, malnutrition, nutritional assessment tools, prognosis, systematic review and meta-analysis**

APPENDIX **For the Search strategy for Medline as well as supplemental tables and figures, please see the online version of this paper.**