Correlations and Prognostic Roles of the Nutritional Status and Neutrophil-to-lymphocyte Ratio in Elderly Patients with Acute Myocardial Infarction Undergoing Primary Coronary Intervention

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Summary

The prognostic capacities of nutritional status and inflammation in patients with acute myocardial infarction (AMI) have attracted increasing interest. However, the combined usefulness of the Controlling Nutritional Status (CONUT) score and neutrophil-to-lymphocyte ratio (NLR) in predicting adverse outcomes has not been investigated. The aim of our study was to investigate the relationship between the CONUT score and the NLR in patients with AMI and assessing the potential of these factors as prognostic markers.

In this retrospective study, we reviewed the medical records of consecutive patients aged 65 years or older who were diagnosed with AMI and who underwent primary coronary intervention. We assessed the nutritional and inflammatory statuses using the CONUT score and the NLR, respectively. The NLR and CONUT score in the major adverse cardiovascular event (MACE) (+) patients were significantly higher than those in the MACE (−) patients. The areas under the receiver operating characteristic curves of the NLR and CONUT score were 0.71 and 0.77, respectively. The Kaplan-Meier analysis showed that patients with a high NLR (≥6.07) and CONUT score (≥3.5) had the worst prognoses. The multivariate Cox proportional hazards analyses suggested that the CONUT score was an independent predictor.

The CONUT score was proven to be a significant prognostic factor of clinical outcomes in patients with AMI. However, further research in this area is needed to more fully understand the relationship among nutritional status, inflammation, and cardiovascular diseases, which might help reduce MACEs in patients with AMI.

Key words: Controlling nutritional status score, Inflammation, Prognosis, Cardiovascular event

Despite the abundant developments in percutaneous coronary intervention (PCI) and other revascularization strategies, acute myocardial infarction (AMI) remains among the leading causes of death worldwide. Numerous risk factors have been shown to be associated with major adverse cardiovascular events (MACEs) in AMI. Among these factors, malnutrition and inflammation are gradually becoming recognized as strong predictors of poor clinical outcomes.

The inflammatory response after myocardial infarction (MI) may promote adverse left ventricular remodeling and, thus, has prognostic relevance. The roles of leukocyte counts within 24 hours of admission as independent prognostic factors of MACEs in patients with AMI have been investigated in some clinical studies. A study by Takahashi, et al. demonstrated that high concentrations of neutrophils in the peripheral blood were associated with adverse left ventricular remodeling and an impaired prognosis. In another study by Zouridakis, et al., low lymphocyte levels were significantly associated with cardiovascular disease morbidity and mortality. The neutrophil-to-lymphocyte ratio (NLR) indicates changes in both neutrophil and lymphocyte counts, and compared with a single indicator, the NLR has a higher predictive value in the prognosis of patients with AMI.

In addition to other comorbidities, the nutritional status of patients can affect the prognosis of elderly patients. Over the past decade, it has been reported that patients with undernutrition have a higher mortality rate and a longer hospital stay duration than patients with normal nutrition. Studies have found that malnutrition, which is common in patients with cardiovascular disease, is associated with cardiovascular disease prognosis and serious adverse events. The Controlling Nutritional Status (CONUT) score, which includes the serum albumin level, total cholesterol level, and total lymphocyte count, is used to assess the nutritional status and may have major prognostic importance in patients with AMI.

In view of malnutrition-inflammation-atherosclerosis syndrome, malnutrition may be a proxy indicator of inflammation and a risk factor or prognostic indicator of AMI. However, few studies have described this area in...
patients with AMI using appropriate nutritional indices. The aim of our study was to investigate the relationship between the nutritional and inflammatory statuses in patients with AMI and assess the potential of these factors as prognostic markers.

Methods

Study population: In this retrospective study, we reviewed the medical records of consecutive patients who were admitted to the Jiang Yin People’s Hospital with a recorded diagnosis of AMI. Patients who were aged 65 years or older, were diagnosed with AMI, and underwent primary coronary intervention were considered eligible. Baseline data collection was performed between January 1, 2014, and June 30, 2017, and follow-up was conducted until June 30, 2019. The exclusion criteria were active infections, inflammatory diseases (including inflammatory bowel disease, postgastrectomy, and post-enterectomy), significant liver or kidney failure, malignancy, severe valvular heart disease, and missing admission-related hematologic indicators. The local ethics committee approved the study, which was performed in accordance with the Helsinki Declaration.

Data sources and classifications: The data were obtained from the hospital’s computerized medical records. The data included general characteristics (age and sex), risk factors for vascular diseases, disease-related characteristics, MACEs, and interventions administered to treat AMI. The risk factors of vascular diseases included hypertension, diabetes mellitus, dyslipidemia, smoking, and an elevated body mass index (BMI). The disease-related characteristics included the number of involved vessel lesions; the presence of atrial fibrillation as diagnosed by electrocardiogram at admission; prehospital delay time; serum alanine aminotransferase, aspartate aminotransferase, creatinine, blood urea nitrogen, hemoglobin, myocardial troponin I (cTn I), and B-type natriuretic peptide (BNP) levels at admission; the NLR; the CONUT score, including the serum albumin level, total cholesterol level, and total lymphocyte count; left ventricular ejection fraction (LVEF); the performance of PCI; and the administration of medical treatment, including angiotension-converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARBs), beta-blockers, and statins. The MACEs, including death, MI relapse, and hospitalizations due to heart failure, were immediately assessed after admission and up to the terminal point of the 2-year follow-up period. All clinical variables were derived from the hospital’s database, and their detailed definitions have been previously reported.

The nutritional status was assessed using the CONUT score as described in Table I. The serum albumin level was used as an indicator of the protein reserve. The serum total cholesterol level was used as a parameter of caloric depletion. The total lymphocyte count was used as an indicator of impaired immune defenses due to undernutrition. Prefixed ranges of each parameter were assigned scores, and the sum of the scores of the three parameters represented the final CONUT score. Patients with CONUT scores of 0-1, between 2 and 4, and ≥5 reflected normal, mild, and moderate-severe risk of malnutrition, respectively, as described.

Study definitions and endpoint: AMI was diagnosed according to the AHA/ACC guidelines. Patients with systolic blood pressure of ≥140 mmHg and/or diastolic pressure of ≥90 mmHg and those taking antihypertensive agents were considered to have hypertension. Dyslipidemia was defined as a serum LDL-C level of >140 mg/dL, high-density lipoprotein cholesterol level of <40 mg/dL, or the requirement of lipid-lowering agents for treatment. Diabetes mellitus was defined as a fasting glucose level of ≥126 mg/dL, a clinical history of oral hypoglycemic agents, and/or insulin use. The LVEF was measured by echocardiography. All patients were retrospectively followed for 2 years. The study endpoint was the recording of a MACE, including all-cause death, MI, or hospitalization due to congestive heart failure. Patients were divided into the MACE (−) and MACE (+) groups. We investigated whether the inflammatory indicator or nutritional status improved the MACE risk stratification of patients with AMI.

Statistical analysis: Patient characteristics are presented as the median (interquartile) or mean (standard deviation) for continuous variables and n (percent) for categorical data. Before the analysis, all data were subjected to a normality test (Shapiro-Wilk test). Comparisons of the baseline characteristics between the MACE (−) and MACE (+) groups were performed using a two-sided chi-squared test, while differences in the continuous variables were compared using an unpaired t-test or the Mann-Whitney U-test. Correlations between the two study biomarkers and other continuous baseline variables were studied using a nonparametric (Spearman’s) correlation coefficient. The comparison of outcomes among the study patients was performed using a survival analysis. The optimal receiver operating characteristic (ROC) curve cut-off value for MACE prediction was defined as the value maximizing sensitivity and specificity. The Kaplan-Meier curves were calculated from AMI onset to MACE incidence and compared using the log-rank test. In addition, a Cox proportional hazards regression analysis was performed to estimate the relative risks of long-term mortality among the study patients. The multivariate analysis was performed.

Table I. Computation of the Controlling Nutritional Status (CONUT) Score

| Parameter                          | Normal (0-1) | Mild (2-4) | Moderate (5-8) | Severe (9-12) |
|------------------------------------|-------------|-----------|----------------|--------------|
| Albumin, g/dL (score)              | 3.50-4.50 (0)| 3.00-3.49 (2) | 2.50-2.90 (4) | < 2.50 (6)   |
| Total lymphocytes, count/mm³ (score)| > 1600 (0)  | 1200-1599 (1) | 800-1199 (2)  | < 800 (3)    |
| Total cholesterol, mg/dL (score)   | > 180 (0)   | 140-180 (1) | 100-139 (2)   | < 100 (3)    |

CONUT indicates controlling nutritional status.
using all variables with a P-value of <0.15 in the univariate analysis. The Cox regression model included the investigated baseline characteristics that were statistically related to patient outcomes. The statistical analysis was performed using IBM SPSS Statistics 21 and GraphPad Prism 8 software. A P-value of <0.05 was considered statistically significant.

**Results**

The baseline characteristics of the 107 patients with AMI included in this study are summarized in Table II. During the 2-year follow-up period, MACEs, including death (n = 3), MIs (n = 2), and hospitalizations due to heart failure (n = 15), were observed in 20 patients (18.69%). Patients in the MACE (−) group had lower BNP and troponin I levels at admission than patients in the MACE (+) group. In contrast, the MACE (−) patients showed a more efficient ejection fraction, and the CONUT score, the NLR, neutrophil-to-lymphocyte ratio, and DAPT, dual antiplatelet therapy.

When the nutritional status was evaluated by the CONUT score, the NLR increased as the nutritional status declined (P < 0.001, Kruskal-Wallis test). The well-nourished patients had lower median NLR values (4.38), and these values increased linearly as the nutritional status worsened (8.02 in the moderate-severe CONUT score patients). This association was not present when the nutritional status was defined by the BMI (Table III).

As shown in Figure 2, the areas under the ROC curves of the NLR and CONUT score were 0.71 and 0.77, with optimal ROC cut-off points of 6.07 and 3.5, respectively. Additionally, the Kaplan-Meier analysis showed that patients with a high NLR (≥6.07) had worse prognoses than those with a low NLR (≤6.07) (P = 0.002) (Figure 3A), and the same conclusion was reached for patients with a high CONUT score (≥3.5) compared with those with a low CONUT score (<3.5) (P < 0.001) (Figure 3B). Furthermore, patients with a high NLR (≥6.07) and a high CONUT score (≥3.5) had significantly worse prognoses than those with a low NLR (<6.07) and a low CONUT score (<3.5), those with a high NLR and a low CONUT score, those with a low NLR and a high CONUT score, and those with a low NLR and a low CONUT score (log-rank test; P < 0.001, P = 0.030, and P < 0.001, respectively) (Figure 3C).

In the univariate Cox proportional hazards analysis, age (P = 0.116), prehospital delay time (P = 0.026), cTnI levels (P = 0.004), LVEF (P = 0.006), BNP levels (P < 0.001), CONUT scores (P < 0.001) and NLRs (P =

| Table II. Baseline Characteristics of Patients with or without MACEs |

|                | Overall n = 107 | MACE (+) n = 20 | MACE (−) n = 87 | P  |
|----------------|----------------|----------------|----------------|----|
| Age (years)    | 72 (67, 77)    | 76.5 (69.5, 78)| 72 (67, 77)    | 0.109 |
| Male, %        | 86 (80.00)     | 14 (70.00)     | 72 (90.00)     | 0.195 |
| BMI (kg/m²)    | 22.39 ± 1.95   | 22.71 ± 1.74   | 22.31 ± 2.00   | 0.415 |
| Smoking, %     | 45 (42.06)     | 15 (75.00)     | 30 (34.48)     | 0.415 |
| Hypertension, %| 70 (65.42)     | 15 (75.00)     | 55 (63.22)     | 0.318 |
| Dyslipidemia, %| 37 (34.58)     | 3 (15.00)      | 7 (8.05)       | 0.965 |
| Diabetes mellitus, % | 19 (17.76) | 5 (25.00)      | 14 (13.09)     | 0.347 |
| Atrial fibrillation at admission, % | 9 (8.41) | 4 (20.00) | 6 (6.90) | 0.417 |
| Multivessel, % | 63 (58.88)     | 11 (55.00)     | 52 (59.77)     | 0.696 |
| ALT, U/L       | 42.92 ± 26.22  | 49.21 ± 23.03  | 41.47 ± 26.81  | 0.236 |
| AST, U/L       | 194.26 ± 128.71| 212.50 ± 122.65| 190.07 ± 130.38| 0.485 |
| Creatinine, μmol/L | 89.35 ± 24.51 | 93.37 ± 29.72 | 88.43 ± 23.26 | 0.638 |
| BUN, mmol/L    | 6.41 ± 1.95    | 6.59 ± 2.15    | 6.36 ± 1.92    | 0.372 |
| Hemoglobin, g/L| 131.04 ± 20.34 | 134.82 ± 21.06| 130.17 ± 20.19| 0.359 |
| Troponin I at admission, ng/mL | 43.87 (11.57,83.00) | 91.50 (44.35,102.00) | 46.13 (10.69,83.00) | 0.002 |
| Prehospital delay time, hours | 3 (12, 5) | 3.75 (2.25, 7.13) | 3 (2, 5) | 0.094 |
| NLR            | 6.71 ± 2.64    | 8.11 ± 1.92    | 6.39 ± 2.69    | 0.008 |
| CONUT score    | 3.00 (2.00, 4.00) | 4.50 (3.00, 5.00) | 3.00 (1.00, 3.00) | <0.001 |
| BNP (pg/mL)    | 254.00 (132.00,494.30) | 566.70 (404.78,650.75) | 189.00 (99.30,340.00) | <0.001 |
| LV ejection fraction (%) | 52.15 ± 5.53 | 49.15 ± 4.34 | 52.83 ± 5.57 | 0.007 |
| ACE inhibitor/ARB, % | 36 (33.64) | 9 (45.00) | 27 (31.03) | 0.233 |
| Beta-blockers, % | 65 (60.75) | 11 (55.00) | 54 (62.07) | 0.559 |
| Statin, %      | 102 (95.33)    | 18 (90.00)     | 84 (96.55)     | 0.213 |
| Duration of DAPT, months | 12.00 (12.00, 12.50) | 12.00 (8.50, 12.00) | 12.00 (12.00, 12.50) | 0.095 |

Values are reported as the number (%), mean ± standard deviation, or median (25th, 75th percentiles). ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; CONUT, controlling nutritional status; BUN, blood urea nitrogen; LV, left ventricular; MACEs, major adverse cardiac events (including all-cause death, myocardial infarction, and hospitalization due to congestive heart failure); NLR, neutrophil-to-lymphocyte ratio; and DAPT, dual antiplatelet therapy.
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NUTRITIONAL STATUS AND THE NLR IN AMI PATIENTS

Figure 1. The CONUT scores (A) and NLRs (B) of patients with or without MACEs. CONUT indicates controlling nutritional status; and NLR, neutrophil-to-lymphocyte ratio.

Table III. NLR Variation According to Nutritional Status

| Nutritional status | NLR         | P*       |
|--------------------|-------------|----------|
| BMI (kg/m²)        |             |          |
| Underweight        | 4.57 (3.58, 6.99) | 0.175    |
| Normal             | 6.16 (4.38, 8.74) |          |
| Overweight         | 7.24 (5.91, 8.29) |          |
| Obese              | 7.86 (5.26, 9.36) |          |
| CONUT score        | < 0.001     |          |
| Normal             | 4.38 (3.07, 6.16) |          |
| Mild               | 7.14 (5.22, 9.27) |          |
| Moderate-severe    | 8.02 (6.45, 8.31) |          |

*Kruskal-Wallis test. BMI indicates body mass index; and CONUT, controlling nutritional status.

0.009) were significantly associated with MACEs (Table IV). According to the multivariate Cox proportional hazards analyses that included all variables with P < 0.15 in the univariate analysis, high cTn I levels, BNP levels, and CONUT scores independently predicted MACEs (Table IV).

Discussion

In the present study, we evaluated the associations between nutritional and inflammatory statuses and between these factors and clinical outcomes in patients with AMI. Our key findings are as follows. First, high CONUT scores and NLRs may be used to predict adverse clinical outcomes and mortality in patients with AMI. Second, the CONUT score is an independent predictor of MACEs in patients with AMI, and a combined analysis of the CONUT score and NLR may improve the risk stratification of MACEs. Third, malnutrition may be a proxy indicator of inflammation, suggesting that greater attention should be paid to individualized therapeutic targets for dyslipidemia in elderly populations at a high risk of malnutrition.

The hypothesis that atherosclerosis drives MACEs has gained accumulating evidence in cardiology over the past 20 years. Inflammation is fully engaged in all stages of atherosclerosis from endothelial dysfunction, immune cell aggregation, low-density lipoprotein modifications, and foam cell formation and apoptosis to complications of acute thrombosis triggered by plaque rupture or plaque erosion. High-sensitivity C-reactive protein (hs-CRP), as one of the objective indicators of the body's inflammatory response, is synthesized by the liver under the induction of interleukin-6 and has been confirmed by numerous studies to be related to the severity and prognosis of MI. Compared to hs-CRP, NLR is a new inflammatory response index, with the advantages of a more convenient measurement method, better cost-effectiveness, better repeatability, and easier promotion in grassroots and community hospitals. Research has shown that neutrophils induce and activate inflammatory responses, while lymphocytes have anti-inflammatory functions and protect the endothelium, and destruction of the balance between neutrophils and lymphocytes is the basis for the occurrence of inflammatory reactions. Therefore, a higher NLR indicates a more intense inflammatory response. As an established biomarker of systemic inflammation, the NLR has been strongly associated with morbidity and mortality in a wide range of cardiovascular diseases, including AMI, in recent reports. Tahto et al. revealed that the average NLR values in patients with AMI were significantly higher than those in patients with unstable angina, highlighting the importance of this inflammatory marker in the discrimination of the clinical forms of acute coronary syndrome. Coincidentally, Hong et al. studied 309 patients with AMI who underwent cardiac magnetic resonance (CMR) imagining and complete blood cell counts within 24 hours before and after PCI and found that a high post-PCI NLR value was associated with an increased risk of large-sized infarction as measured by CMR and adverse clinical outcomes, indicating a considerable prognostic significance for the post-PCI NLR in patients with AMI. Although our research found that the NLR was not an independent factor due to our limited number of patients, links between inflammation and cardiovascular diseases are worthy of launching additional clinical trials aiming to test whether drugs that primarily target inflammation can reduce cardiovascular events.

Furthermore, our study shows that, in addition to the BNP and cTn I levels, the CONUT score, which includes the serum albumin level, total cholesterol level, and total
lymphocyte count and is used for assessing the nutritional status, has an independent impact on the prognosis of elderly patients with AMI. Concordantly, Sung et al. investigated 2251 patients screened from the Korea Acute Myocardial Infarction Registry database and found that the nutritional status that was based on geriatric nutritional risk index scoring was a significant prognostic factor of clinical outcomes after MI, indicating that nutritional assessment and intervention should be considered, especially in undernourished MI patients. In our study population, which was predominantly composed of elderly patients (>65 years), a malnutrition status was strongly associated with BNP levels, confirming the unquestionable relationship between malnutrition and heart failure severity.

Through this study, we know that baseline undernutrition measured by the CONUT score is a prognostic factor of poor clinical outcomes in patients with AMI. In the future, additional studies are needed to further validate whether the CONUT score is a useful nutritional assessment tool regardless of chronological changes due to the disease state.

Furthermore, in our study, the NLR was associated with the CONUT score (Table III). As patients’ nutritional state worsened, the NLR increased. The association among poor nutrition, inflammation, and atherosclerosis is undoubtedly complicated. Stenvinkel proposed malnutrition-inflammation-atherosclerosis syndrome, suggesting that inflammation may promote general catabo-
lism, stimulate protein degradation, and inhibit protein synthesis, causing malnutrition, while malnutrition can aggravate inflammation. Moreover, malnutrition can weaken immune defenses, rendering patients more susceptible to infection and thus causing an inflammatory response.15,16) Therefore, malnutrition and inflammation are mutually causal and vicious, and jointly promote the development of cardiovascular disease.

Finally, the present study notes that existing clinical trials mostly have limited enrolment of elderly populations, and therapeutic schedules that are effective in younger patients are usually recommended for older patients, with the caveat that these treatments can cause serious side effects. Our results suggest that the therapeutic targets for dyslipidemia must be individualized in this elderly population at a high risk of malnutrition.

Several limitations of this study should be acknowledged. First, our study represents a single-hospital experience with a limited number of patients. Additional multicenter, randomized studies with larger sample sizes should be conducted to support these results. Second, we analyzed indicator levels only at admission, resulting in a short follow-up duration. Measurements of the CONUT score and NLR over a longer time course may provide additional information regarding clinical outcomes.

In conclusion, this study revealed the potential value of the CONUT score as an indicator of the prognosis of AMI. Further research in this area is needed to more fully understand the relationship among the nutritional status, inflammation, and cardiovascular diseases, which could help reduce MACEs in patients with AMI.

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Disclosure

Conflicts of interest: We received no financial support for this study. The authors declare that there are no conflicts of interest regarding the publication of this paper.

Statement of ethics: We state that all subjects provided informed consent and that the study protocol was approved by the institute’s committee on human research.

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Table IV. Predictors of the 2-Year Incidence of MACEs by a Multivariate Cox Regression Analysis

| Variables | Hazard ratio (95% confidence interval) | No adjustment | P | Adjustment | P |
|-----------|-------------------------------|---------------|---|------------|---|
| Age       | 1.051 (0.988, 1.119)          | 0.116         | 1.004 (0.926, 1.089) | 0.914 |
| Prehospital delay time, hours | 1.158 (1.018, 1.318) | 0.026 | 1.048 (0.893, 1.231) | 0.565 |
| cTn I     | 1.021 (1.007, 1.036)          | 0.004         | 1.017 (1.001, 1.033) | 0.033 |
| LVEF      | 0.890 (0.820, 0.966)          | 0.006         | 0.914 (0.832, 1.004) | 0.062 |
| BNP       | 1.004 (1.002, 1.005)          | <0.001        | 1.002 (1.001, 1.004) | 0.010 |
| NLR       | 1.237 (1.053, 1.453)          | 0.009         | 1.059 (0.827, 1.355) | 0.652 |
| CONUT score | 1.474 (1.197, 1.815) | <0.001 | 1.402 (1.053, 1.868) | 0.021 |

Adjusted for age; diabetes mellitus, hypertension, dyslipidemia, smoking, creatinine level, cTn I level, LVEF, BNP level, NLR, and CONUT score. BNP indicates B-type natriuretic peptide; CO-NUT, controlling nutritional status; cTn I, cardiac troponin I; LVEF, left ventricular ejection fraction; and NLR, neutrophil-to-lymphocyte ratio.
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