CLINICAL STUDY

Association of GNRI, NLR, and FT3 with the Clinical Prognosis of Older Patients with Heart Failure

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Summary

We investigated the relationship between heart failure and malnutrition, inflammation, and thyroid function and evaluated the predictive potential of these markers for major adverse cardiovascular events (MACEs).

This study included 454 patients aged over 65 years with heart failure as the main diagnosis for 18 months follow-up. The nutritional and inflammatory status were assessed using the geriatric nutritional risk index (GNRI) and neutrophil-to-lymphocyte ratio (NLR), respectively. Free triiodothyronine (FT3) in thyroid hormone was divided into low, medium, and high FT3. Older patients were divided into two groups according to whether they had endpoint events. Differences in nutrition, inflammation, and thyroid hormone were compared between the two groups. The prognostic value of the combination of GNRI, NLR, and FT3 was analyzed.

Older patients in the MACEs (+) group had lower levels of GNRI and FT3 and higher NLR than those in the MACEs (−) group. Low GNRI and FT3 and high NLR were associated with MACEs ($P < 0.05$). Multivariate Cox regression analysis revealed that low FT3 was an independent predictor of MACEs ($P < 0.05$). Regardless of how the LVEF changed, when patients had low GNRI and FT3 and high NLR risk factors, the risk of developing MACEs significantly increased. The addition of GNRI, NLR, and FT3 to the basic model significantly increased the predictability of MACEs in patients.

Low GNRI and FT3 and high NLR were associated with MACEs. The combination of GNRI, NLR, and FT3 increased the predictive value of MACEs in older patients with heart failure.

Key words: Major adverse cardiovascular event, Malnutrition, Inflammation, Thyroid function, Risk factor

Heart failure is a clinical syndrome caused by a structural or functional disorder of the heart that impairs ventricular filling or ejection, resulting in insufficient perfusion of blood to tissues and organs.\textsuperscript{1)} Patients with heart failure frequently have recurrent clinical episodes and a high rate of readmissions and mortality. Due to increased life expectancy and an aging society, nearly 20\% of our patients are hospitalized for heart failure, and approximately 80\% of heart failure hospitalizations are for patients over the age of 65, which is strongly associated with poor outcomes.\textsuperscript{2,3)}

Malnutrition is considered a common complication in patients with heart failure and is a strong predictor of the occurrence of adverse clinical outcomes.\textsuperscript{4,5)} Despite the fact that obesity is a common risk factor for cardiovascular disease, patients with heart failure who have a higher body mass index (BMI) have a better chance of survival.\textsuperscript{6)} The geriatric nutritional risk index (GNRI) is a screening tool used for assessing the nutritional status of older people. It is primarily composed of serum albumin and BMI.\textsuperscript{7)} Heart failure with low GNRI is linked to an increased all-cause mortality.\textsuperscript{8)} The systemic proinflammatory state is a major contributor to the cardiac pathology of heart failure, resulting in irreversible heart damage.\textsuperscript{9)} The neutrophil-to-lymphocyte ratio (NLR) as an indicator of combined inflammation is strongly linked to mortality in a variety of cardiovascular diseases.\textsuperscript{10)} During heart failure, NLR is associated with multiple inflammatory markers associated with inflammatory pathways, and it represents a nonspecific inflammatory and physiological stress response.\textsuperscript{11)} Moreover, patients with heart failure are frequently associated with thyroid dysfunction, which has been shown to increase the risk of death in patients,\textsuperscript{12)} particularly with low levels of free triiodothyronine (FT3), significantly prolonging the patient’s hospital stay and negatively impacting hospital outcomes.\textsuperscript{13)} In patients who already have heart failure, the lack of sufficient heart capacity to tolerate minor changes in the thyroid hormone increases the incidence of adverse events in patients.\textsuperscript{14)}

B-type natriuretic peptide (BNP) is often used as a biomarker of clinical diagnosis in heart failure, but in older patients, the threshold for natriuretic peptide is increased, and the accuracy of prognosis assessment is reduced.\textsuperscript{15)} Further research is needed to determine whether the accuracy of the prognostic assessment of heart failure in the elderly can be improved by combining multiple...
other indicators. Therefore, in this study, the aim was to investigate the relationship between GNRI, NLR, and FT3 and the clinical prognosis of older patients with heart failure and whether the combination of the three has a better value potential in predicting the occurrence of major adverse cardiovascular events (MACEs) in patients.

Methods

Subjects: In this observational retrospective cohort study, 644 consecutive patients hospitalized at Shanghai Fifth People’s Hospital, Fudan University, between January 2017 and December 2019 with heart failure as their primary diagnosis were included. Finally, a total of 454 elderly patients (age 65 and older) with heart failure were analyzed. Heart failure was defined as worsening of the clinical symptoms/signs of congestion and peripheral hypoperfusion according to the European Society of Cardiology guidelines. The main manifestations were dyspnea, physical limitation, and fluid retention. Physical examination may be accompanied by enlargement of the cardiac boundary, galloping of the heart or wet rales in the lungs, and depressed edema of both the lower limbs. The exclusion criteria were as follows: (1) congenital heart disease, constrictive pericarditis, heart transplantation, infective endocarditis, and malignant arrhythmia; (2) acute coronary syndrome, coronary revascularization, and glucocorticoid therapy within 3 months; (3) use of amiodarone or dopamine, thyroid hormone, or derivatives prior to hospitalization, a history of hyperthyroidism or hypothyroidism, and having had thyroid surgery; (4) active infectious disease, active malignancy, cirrhosis of the liver, hemodialysis or peritoneal dialysis, and chronic inflammatory diseases; (5) invasive mechanical ventilation, emergency transfusion of severe anemia, and hematopoietic disorders; (6) BNP < 100 ng/L; and (7) incomplete medical history and missing follow-up. All patients were given a routine and acceptable optimal treatment regimen during hospitalization in accordance with the heart failure guidelines. This study was approved by the hospital’s ethics review board and adhered to the basic tenets of the Declaration of Helsinki.

Study protocol: Basic clinical information and clinical complications upon admission were obtained from the history system records. The corresponding laboratory parameters were obtained using conventional laboratory methods at our hospital. Left ventricular ejection fraction (LVEF) was recorded via echocardiography. Heart failure is classified into three types according to the level of LVEF: LVEF < 40%, heart failure with reduced ejection fraction (HFrEF); LVEF between 40% and 49%, heart failure with mid-range ejection fraction (HFmrEF); and LVEF ≥ 50%, heart failure with preserved ejection fraction (HFpEF).

Follow-up: The patients were followed up for 18 months by medical records, recording the main causes of death during the period and following up until July 2021. The MACEs were heart failure readmission or cardiac death within 18 months following discharge, and the survival time was recorded. The subjects were divided into the MACEs (+) and MACEs (−) groups based on whether a primary endpoint was present. The analysis process in this study mainly follows the process presented in Figure 1.

Inflammatory and nutritional assessment: NLR and GNRI were used to evaluate the inflammatory and nutritional status, respectively. Height and weight were measured, and the BMI was calculated. The calculation formula of GNRI was as follows: GNRI = 14.89 × albumin (g/dL) + 41.7 × BMI/22. A GNRI score ≤ 98 was considered an indicator of malnutrition, defined as a low GNRI. NLR was calculated as the ratio of absolute neutrophils to absolute lymphocytes. The optimal cutoff point of the NLR determined by the receiver operating characteristic curve was 2.53, and high NLR was defined as NLR > 2.53.

Statistical analysis: All variables were tested for normal distribution using the Shapiro-Wilk test; continuous variables were expressed as mean ± standard deviation or median (interquartile), and the categorical variables were expressed as numbers (percentage). The independent sample t-test or the Mann-Whitney U test was used to compare continuous variables and two-sided chi-squared test to compare categorical variables. Cox regression analysis assessed the relative risk of FT3, GNRI, and NLR on patients developing MACEs (including cardiac death and readmission due to heart failure), adjusting for age, LVEF,
BNP, and estimated glomerular filtration rate (eGFR) in a multivariate analysis. Kaplan-Meier curves were used to assess the difference in survival between groups with FT3, GNRI, and NLR as risk factors, and comparative analysis was conducted using a log-rank test. Cox regression analysis was employed to assess the relative risk of FT3, GNRI, and NLR as risk factors for the development of MACEs in patients with heart failure in different LVEF groups. All baseline variables with \( P < 0.05 \), determined by univariate analysis, were entered into multivariate analysis. The area under the ROC curve (AUC) was used to compare the potential value of the base model and the stepwise addition of NLR, GNRI, and FT3 for predicting MACEs. Statistical analysis was conducted using IBM SPSS statistics 23.0 and MedCalc statistics v20.0.4, with a \( P \) value < 0.05 considered statistically significant.

Results

Baseline characteristics of patients: During the 18-month follow-up period, 236 patients developed MACEs, including cardiac death (\( n = 42 \)) and readmission due to heart failure (\( n = 221 \)). The mean age of the patients was 76 ± 8 years, of which 247 (54.4%) were men. Older patients and those with poor renal function were more likely to develop MACEs. Compared with patients with MACEs (−), those with MACEs (+) had higher BNP (\( P < 0.001 \)) levels and lower systolic blood pressure (\( P = 0.016 \)), triglyceride level (\( P = 0.038 \)), hemoglobin level (\( P = 0.002 \)), and LVEF (\( P < 0.001 \)). For thyroid function, patients with MACEs (+) had a lower FT3 level (\( P < 0.001 \)) than those with MACEs (−), whereas the difference between FT4 and TSH was not significant. Patients with MACEs (+) had lower BMI (\( P = 0.011 \)), serum albumin (\( P < 0.001 \)), and GNRI score (\( P < 0.001 \)) than those with MACEs (−). The prevalence of malnutrition was significantly higher in patients with MACEs (+) than in those with MACEs (−) (\( P < 0.001 \)). For inflammatory markers, patients with MACEs (+) had higher neutrophil count (\( P < 0.001 \)) and NLR (\( P < 0.001 \)) than those with MACEs (−); however, the lymphocyte count was lower (\( P < 0.001 \)) (Table I).

Prediction effect of GNRI, NLR, and FT3 on MACEs: The three risk factors were divided into low NLR (\( 
\leq 2.53 \)), medium NLR (\( > 2.53 \) and \( \leq 76 \)), and high NLR (> 76). The GNRI score divided into low GNRI (\( \leq 98 \)) and high GNRI (> 98) in two groups. The NLR score was divided into low NLR (\( < 0.05 \)) and high NLR (\( \geq 0.05 \)) in two groups. All were entered into the Cox regression analysis model as categorical variables. In the univariate Cox regression model, low GNRI, low FT3, and high NLR were the main risk factors for MACEs (\( P < 0.01 \)). Low FT3 levels remained an independent risk factor for MACEs after adjustment for age, LVEF, BNP, and eGFR (\( P < 0.05 \)). Contrarily, low GNRI was only associated with cardiac death (\( P = 0.025 \)), and high NLR was only associated with readmission due to heart failure (\( P = 0.001 \)) (Table II).

The survival rates of the different groups were compared using the Kaplan-Meier curve according to the number of these three risk factors (FT3 < 3.74, GNRI ≤ 98, and NLR > 2.53). The rates of cardiac mortality were 0.0%, 7.07%, 15.96%, and 31.82% in patients with no risk factor, any one risk factor, any two risk factors, and all risk factors, respectively (\( P < 0.001 \)) (Figure 2A), and a similar trend was observed in heart failure readmission and overall MACE incidence among the four groups (Figure 2B and C). In the Cox regression analysis, regardless of the change in the LVEF values, having three risk factors was significantly associated with the risk of developing MACEs (\( P < 0.05 \)) (Table III).

For the basic model (including age, sex, LVEF, systolic blood pressure, BNP, eGFR, hemoglobin, triglyceride, history of coronary heart disease, and diabetes), the AUC for predicting MACEs in patients with heart failure was 0.766 (\( P < 0.001 \)). Adding low GNRI, NLR, and FT3 to the basic model alone can increase the predictability of MACEs (\( P < 0.001 \)). When low GNRI, NLR, and FT3 were added to the basic model simultaneously, the AUC increased from 0.766 to 0.802 (\( P < 0.001 \)), and the incremental change value was 3.70% (\( P = 0.007 \)), which significantly improved the overall prediction level of the model (Table IV).

Discussion

The main findings of this study were as follows: (1) Older heart failure patients with MACEs had lower GNRI and FT3 and higher NLR. (2) Low GNRI and FT3 and high NLR were the main risk factors for MACEs, and low FT3 was an independent predictor of poor prognosis. (3) Regardless of the change in the LVEF values, having three risk factors was significantly associated with the risk of developing MACEs. (4) The combination of GNRI, NLR, and FT3 significantly increased the predictive value of MACEs in older patients with heart failure and increased the risk stratification ability of the model.

In this study, malnutrition was present in 23.6% of heart failure patients, with the primary endpoint event occurring in 74.8% of these patients. Malnutrition is often associated with a high catabolic state, causing loss of body muscle mass and weight.\(^{19,26,27}\) There is an “obesity paradox” in heart failure patients, with patients having a better survival profile at higher BMI and an increased risk of death when they are underweight or overweight.\(^{18,21}\) Serum albumin is often involved in the anti-inflammatory, antioxidant, and anticoagulant processes in the acute phase of the body and is associated with the incidence of long-term adverse cardiovascular events.\(^{28}\) It has been demonstrated that GNRI is a better predictor of poor prognosis in patients with heart failure than any other model comparing BMI, serum albumin, and GNRI.\(^{19}\) In a study of 213 elderly heart failure patients aged ≥ 80 years, mortality was found to be significantly higher in the low GNRI group than in the normal GNRI group and was significantly associated with poor prognosis.\(^{20}\) Furthermore, GNRI has a better overall prevalence of malnutrition than other nutritional screening tools, resulting in the largest incremental value for predicting adverse outcomes in patients with heart failure.\(^{21}\) In malnourished patients with heart failure, the heart function was worse, they suffered from more symptoms of heart failure, and peripheral circulation congestion was more common.\(^{22}\) A combination
The older heart failure patients can reduce the rates of mortality and readmission in patients with heart failure. The older heart failure patients also play an important role in the progression of heart failure, inducing cardiac fibrosis and pathological remodeling. Neutrophil to lymphocyte ratio (NLR) is a combination of neutrophil and lymphocyte, and pathologically elevated NLR predicts the risk of adverse outcome events in patients with cardiovascular disease. In studies with different chronic heart failure ejection fractions, the heart failure symptoms were more severe in patients with NLR above the median, and patients with heart failure in the highest NLR had the worst prognosis regardless of LVEF stratification when the NLR was trisected. Neutrophils are closely associated with the development of cardiovascular disease, contributing to atherosclerosis and thrombosis and recruiting other inflammatory cells by shedding associated interleukin receptors and activating endothelial cells. Lymphocyte-mediated immune inflammatory responses also play an important role in the progression of heart failure, inducing cardiac fibrosis and pathological remodeling. NLR is a combination of neutrophil and lymphocyte ratio. BMI, body mass index; GNRI, geriatric nutritional risk index; ARNI, angiotensin receptor-neprilysin inhibitor; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; LVDd, left ventricular diastolic dimension; LVSd, left ventricular systolic dimension; ISWT, interventricular septal wall thickness; and PWT, posterior wall thickness.

### Table 1. Baseline Characteristics of Patients with or without MACEs

|                      | Overall          | MACEs (+)        | MACEs (−)        | P     |
|----------------------|------------------|------------------|------------------|-------|
|                      | n = 454          | n = 236          | n = 218          |       |
| Age (years)          | 76 ± 8           | 77 ± 8           | 75 ± 7           | 0.025 |
| Male, n (%)          | 247 (54.4)       | 131 (55.5)       | 116 (53.2)       | 0.623 |
| LVEF (%)              | 57 (40–63)       | 45 (36–60)       | 60 (48–65)       | < 0.001 |
| HFrEF, n (%)          | 262 (57.8)       | 103 (43.8)       | 159 (72.9)       | < 0.001 |
| HfmrEF, n (%)         | 85 (18.8)        | 58 (24.7)        | 27 (12.4)        | 0.001 |
| HfEF, n (%)           | 106 (23.4)       | 74 (31.5)        | 32 (14.7)        | < 0.001 |
| Smoking history, n (%)| 101 (22.2)       | 54 (22.9)        | 47 (21.6)        | 0.735 |
| Systolic blood pressure (mmHg) | 132.75 ± 19.24 | 130.66 ± 19.19 | 135.01 ± 19.08 | 0.016 |
| Hypertension, n (%)   | 346 (76.2)       | 184 (78.0)       | 162 (74.3)       | 0.361 |
| Coronary heart disease, n (%) | 200 (44.1) | 112 (47.5) | 88 (40.4) | 0.128 |
| Diabetes mellitus, n (%) | 146 (32.2) | 83 (35.2) | 63 (28.9) | 0.153 |
| Atrial fibrillation, n (%) | 243 (53.5) | 131 (55.5) | 112 (51.4) | 0.378 |
| BNP (pg/mL)           | 1985.00 (655.75–4682.50) | 2915.00 (1390.00–7637.50) | 1160.00 (378.50–2692.50) | < 0.001 |
| Creatinine (umol/L)   | 91 (73–115)      | 99 (80–136)      | 84 (68–100)      | < 0.001 |
| eGFR (mL/(min·1.73 m²)) | 61.55 ± 22.03   | 54.77 ± 22.58    | 68.37 ± 19.24    | < 0.001 |
| Total cholesterol (mmol/L) | 3.68 ± 1.03     | 3.61 ± 1.06      | 3.75 ± 0.99      | 0.153 |
| Triglycerides (mmol/L) | 1.07 (0.81–1.44) | 1.04 (0.78–1.36) | 1.14 (0.82–1.62) | 0.038 |
| Hemoglobin (g/L)      | 126.10 ± 20.25   | 123.34 ± 20.70   | 129.10 ± 19.36   | 0.002 |
| T3 (nmol/L)           | 1.37 ± 0.37      | 1.27 ± 0.37      | 1.47 ± 0.33      | < 0.001 |
| T4 (nmol/L)           | 97.55 ± 22.29    | 98.88 ± 23.95    | 96.11 ± 20.30    | 0.187 |
| FT3 (pmol/L)          | 4.05 ± 1.12      | 3.76 ± 1.06      | 4.36 ± 1.28      | < 0.001 |
| FT4 (pmol/L)          | 17.80 ± 4.23     | 18.10 ± 3.97     | 17.46 ± 4.47     | 0.108 |
| TSH (mIU/L)           | 2.52 (1.56–4.12) | 2.40 (1.45–4.14) | 2.74 (1.66–4.10) | 0.118 |
| Neutrophils (10⁹/L)   | 4.07 ± 1.60      | 4.40 ± 1.75      | 3.72 ± 1.33      | < 0.001 |
| Lymphocytes (10⁹/L)   | 1.50 ± 0.56      | 1.39 ± 0.51      | 1.63 ± 0.58      | < 0.001 |
| NLR                   | 2.62 (1.89–3.72) | 3.03 (2.21–4.27) | 2.27 (1.61–5.05) | < 0.001 |
| Albumin (g/L)         | 39.71 ± 4.73     | 38.63 ± 4.63     | 40.89 ± 4.56     | < 0.001 |
| BMI (kg/m²)           | 24.38 ± 3.87     | 23.93 ± 3.80     | 24.86 ± 3.89     | 0.011 |
| GNRI                  | 105.34 ± 10.89   | 102.88 ± 11.19   | 107.99 ± 9.92    | < 0.001 |
| GNRI ≤ 98, n (%)      | 107 (23.6)       | 80 (33.9)        | 27 (12.4)        | < 0.001 |
| ARNI, n (%)           | 30 (6.6)         | 22 (9.3)         | 8 (3.7)          | 0.022 |
| Beta-blockers, n (%)  | 305 (67.2)       | 161 (68.2)       | 144 (66.1)       | 0.689 |
| ACEI/ARB, n (%)       | 228 (50.2)       | 109 (46.2)       | 119 (54.6)       | 0.075 |
| Diuretics, n (%)      | 331 (72.9)       | 197 (83.5)       | 134 (61.5)       | < 0.001 |
| LVDd (mm)             | 52.00 (46.00–58.00) | 55.00 (48.00–62.00) | 50.00 (45.00–55.00) | < 0.001 |
| LVSd (mm)             | 36.00 (30.00–46.00) | 40.00 (32.00–50.00) | 32.00 (29.00–40.00) | < 0.001 |
| ISWT (mm)             | 9.63 ± 1.51      | 9.74 ± 1.76      | 9.52 ± 1.17      | 0.109 |
| PWT (mm)              | 9.39 ± 1.11      | 9.49 ± 1.16      | 9.28 ± 1.04      | 0.040 |

Values were expressed as mean ± standard deviation, number (%), or median (interquartile range). MACE indicates major adverse cardiovascular events; LVEF, left ventricular ejection fraction; HFrEF, heart failure with preserved ejection fraction; HfmrEF, heart failure with mid-range ejection fraction; HfEF, heart failure with reduced ejection fraction; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; T3, triiodothyronine; T4, thyroxine; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone; NLR, neutrophil to lymphocyte ratio; BMI, body mass index; GNRI, geriatric nutritional risk index; ARNI, angiotensin receptor-neprilysin inhibitor; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; LVDd, left ventricular diastolic dimension; LVSd, left ventricular systolic dimension; ISWT, interventricular septal wall thickness; and PWT, posterior wall thickness.
Table II. Cox Regression Analysis of the Risk Ratios for MACEs

|                     | Univariate analysis |          | Multivariate analysis |          |
|---------------------|---------------------|----------|-----------------------|----------|
|                     | HR (95% CI)         | P        | HR (95% CI)           | P        |
| Cardiac death       |                     |          |                       |          |
| GNRI (≤ 98)         | 5.28 (2.86–9.73)    | < 0.001  | 2.56 (1.13–5.81)      | 0.025    |
| NLR (> 2.53)        | 3.02 (1.52–6.03)    | 0.002    | 1.20 (0.56–2.61)      | 0.640    |
| FT3 (pmol/L)        |                     |          |                       |          |
| High (> 4.31)       | Reference           |          | Reference             |          |
| Middle (3.74–4.31)  | 0.86 (0.26–2.81)    | 0.799    | 0.83 (0.21–3.35)      | 0.791    |
| Low (< 3.74)        | 7.22 (3.00–17.40)   | < 0.001  | 3.27 (1.04–10.32)     | 0.043    |
| Readmission due to heart failure | | | | |
| GNRI (≤ 98)         | 2.13 (1.60–2.83)    | < 0.001  | 1.36 (0.95–1.93)      | 0.090    |
| NLR (> 2.53)        | 2.27 (1.72–3.01)    | < 0.001  | 1.75 (1.26–2.42)      | 0.001    |
| FT3 (pmol/L)        |                     |          |                       |          |
| High (> 4.31)       | Reference           |          | Reference             |          |
| Middle (3.74–4.31)  | 1.22 (0.85–1.76)    | 0.273    | 1.37 (0.91–2.06)      | 0.133    |
| Low (< 3.74)        | 2.82 (2.02–3.92)    | < 0.001  | 2.23 (1.48–3.36)      | < 0.001  |

Adjusted for age, left ventricular ejection fraction, B-type natriuretic peptide, estimated glomerular filtration rate. FT3 indicates free triiodothyronine; NLR, neutrophil to lymphocyte ratio; GNRI, geriatric nutritional risk index; and MACE, major adverse cardiovascular events.

leukocyte, neutrophil, and lymphocyte. In this study, we found that Cox regression analysis revealed that high levels of NLR increased the risk of patient recognition of readmission due to heart failure.

The stabilization of thyroid hormones is essential for the maintenance of normal cardiovascular function, and its alteration can lead to impaired myocardial contraction and filling capacity, formation of vascular lipid plaques, and subsequent development of various cardiovascular diseases. Euthyroid sick syndrome is often caused by nonthyroidal disorders, resulting in low levels of circulating thyroid hormone. FT3 is often used as a valid marker to express early thyroid dysfunction. FT3 has been demonstrated as a strong independent predictor of cumulative death in cardiovascular disease, increasing the predictive value of cumulative death at low concentrations. Low T3 syndrome is more common in heart failure patients with reduced ejection fraction, and lower FT3 levels are associated with lower survival and disease severity. The probability of low T3 levels is increased in older patients with heart failure, with a higher risk of adverse outcomes. In patients with heart failure, low FT3 levels may indicate a metabolic disorder during progressive deterioration of heart function and may predict negative outcomes. This study demonstrated that older heart failure patients with poorer prognosis had lower T3 and FT3 levels. Cox regression analysis revealed that low FT3 levels were associated with both cardiac death and readmission due to heart failure.

In this study, stratification by the number of risk factors, GNRI, NLR, and FT3 predicted MACEs in older patients with heart failure. The study demonstrated that the combined predictive value of the indicators GNRI, NLR, and FT3 (AUC = 0.736) was better than the predictive value of BNP alone (AUC = 0.716). The combination of these three factors can reflect not only the nutritional and inflammatory status of patients with heart failure but also the homeostasis and metabolic status of the patients’ internal environment. Contrarily, thyroid function, inflammation, and malnutrition may not have a single effect on the body but rather interact and cause each other to accelerate disease progression. A prospective clinical study showed that nutritional support had a better effect in patients with low baseline levels of inflammation at admission, whereas there was no significant increase in patient benefit from nutritional support at high baseline levels of inflammation. Decreased levels of serum T3 can also reverse the inflammatory response of cardiovascular injury, which correlates with the severity of many cardiovascular diseases and increase the likelihood of cardiac complications. The indicators of this study are easy to obtain, the cost is low, the clinical repeatability is good, and the method has a certain research value.

This study has limitations that need to be acknowledgment.
Table III. Assessment of MACEs in Different LVEF Groups According to the Number of Risk Factors

|                   | Univariate analysis | Multivariate analysis |
|-------------------|---------------------|-----------------------|
|                   | HR (95% CI)         | P                     | HR (95% CI)         | P                     |
| Overall (versus no risk factor) |                   |                       |                     |                       |
| Any one risk factor | 2.56 (1.72–3.83)    | < 0.001               | 2.47 (1.52–4.00)    | < 0.001               |
| Any two risk factors | 5.42 (3.57–8.25)    | < 0.001               | 4.75 (2.80–8.08)    | < 0.001               |
| All risk factors   | 7.59 (4.73–12.18)   | < 0.001               | 5.78 (3.08–10.85)   | < 0.001               |
| HFpEF group (versus no risk factor) |                   |                       |                     |                       |
| Any one risk factor | 2.82 (1.60–4.97)    | < 0.001               | 2.87 (1.37–6.00)    | 0.005                 |
| Any two risk factors | 5.38 (2.90–9.97)    | < 0.001               | 4.97 (2.18–11.34)   | < 0.001               |
| All risk factors   | 8.23 (3.87–17.46)   | < 0.001               | 5.13 (1.88–14.01)   | 0.001                 |
| HFmrEF group (versus no risk factor) |                   |                       |                     |                       |
| Any one risk factor | 4.62 (1.74–12.25)   | 0.002                 | 6.38 (1.81–22.48)   | 0.004                 |
| Any two risk factors | 7.74 (2.86–20.91)   | < 0.001               | 11.01 (2.68–45.33)  | 0.001                 |
| All risk factors   | 8.13 (2.82–23.44)   | < 0.001               | 12.59 (2.86–55.45)  | 0.001                 |
| HFrEF group (versus no risk factor) |                   |                       |                     |                       |
| Any one risk factor | 1.24 (0.61–2.54)    | 0.552                 | 1.23 (0.54–2.83)    | 0.618                 |
| Any two risk factors | 2.94 (1.44–6.01)    | 0.003                 | 2.19 (0.91–5.28)    | 0.080                 |
| All risk factors   | 3.73 (1.68–8.33)    | 0.001                 | 3.92 (1.33–11.59)   | 0.013                 |

Adjusted for age, systolic blood pressure, left ventricular ejection fraction, B-type natriuretic peptide, estimated glomerular filtration rate, triglycerides, and hemoglobin. MACE indicates major adverse cardiovascular events; LVEF, left ventricular ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; and HFrEF, heart failure with reduced ejection fraction.

Table IV. Discrimination of Each Predictive Model of MACEs

|                   | AUC (95%CI) | P       | △ changes | P     |
|-------------------|------------|---------|-----------|-------|
| The basic model   | 0.766 (0.718–0.808) | < 0.001 | Reference |       |
| + low GNRI        | 0.776 (0.729–0.818) | < 0.001 | 0.0104 | 0.263 |
| + NLR             | 0.780 (0.733–0.821) | < 0.001 | 0.0140 | 0.119 |
| + FT3             | 0.781 (0.735–0.823) | < 0.001 | 0.0156 | 0.111 |
| + low GNRI + NLR  | 0.793 (0.747–0.838) | < 0.001 | 0.0271 | 0.026 |
| + low GNRI + FT3  | 0.790 (0.744–0.836) | < 0.001 | 0.0244 | 0.042 |
| + NLR + FT3       | 0.792 (0.747–0.838) | < 0.001 | 0.0269 | 0.021 |
| + low GNRI + NLR + FT3 | 0.802 (0.758–0.842) | < 0.001 | 0.0370 | 0.007 |

The basic model includes age, sex, left ventricular ejection fraction, systolic blood pressure, B-type natriuretic peptide, estimated glomerular filtration rate, hemoglobin, triglyceride, and history of coronary heart disease and diabetes. AUC indicates the area under the ROC curve; GNRI, geriatric nutritional risk index; NLR, neutrophil to lymphocyte ratio; FT3, free triiodothyronine; and MACEs, major adverse cardiovascular events.

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Disclosure

Conflicts of interest: On behalf of all authors, this manuscript is published with the consent of all authors, stating that there is no conflict of interest or competition and no related disclosure of financial or non-financial interests.

Ethics: The study protocol was approved by the Ethics
Committee of the Shanghai Fifth People’s Hospital affiliated to Fudan University.

Author contributions: All authors participated in the design of this study. Data collection and analysis were performed by Luqiong Liu, Yangqin Chen. The first draft of the manuscript was written by Luqiong Liu. All authors participated in the review and revision of the manuscript and approved the final version.

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