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Nutritional Risk Index Predicts Mortality in Hospitalized Advanced Heart Failure Patients

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Abstract

Introduction—Hospitalized advanced heart failure (HF) patients are at high risk for malnutrition and death. The Nutritional Risk Index (NRI) is a simple, well-validated tool for identifying patients at risk for nutrition-related complications. We hypothesized that in advanced HF patients from the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial, the NRI would improve risk discrimination for 6-month all-cause mortality.

Methods—We analyzed the 160 ESCAPE index admission survivors with complete follow-up and NRI data, calculated as follows: NRI = (1.519 × discharge serum albumin, g/dL) + {41.7 × discharge weight (kg)/ideal body weight (IBW; kg)}; as in previous studies, if discharge weight > IBW, this ratio was set = 1. The previously developed ESCAPE mortality model includes age, 6-minute walk distance, CPR/mechanical ventilation, discharge beta-blocker prescription and diuretic dose, and discharge serum sodium, blood urea nitrogen, and B-type natriuretic peptide levels. We used Cox proportional hazards modeling for the outcome of 6-month all-cause mortality.

Results—30/160 patients died within 6 months of hospital discharge. The median NRI was 96 (IQR 91-102), reflecting mild-to-moderate nutritional risk. The NRI independently predicted 6-month mortality, with adjusted HR 0.60 (95% CI 0.39-0.93), p=.02) per 10 units, and increased Harrell's c index from 0.74 to 0.76 when added to the ESCAPE model. Body mass index and NRI at hospital admission did not predict 6-month mortality. The discharge NRI was most helpful in patients with high (≥ 20%) predicted mortality by the ESCAPE model, where observed 6-month mortality was 38% in patients with NRI < 100 and 14% in those with NRI >100 (p=0.04).

Conclusions—The NRI is a simple tool that can improve mortality risk stratification at hospital discharge in hospitalized patients with advanced HF.

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Disclosures

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Introduction

Advanced heart failure (HF) patients are characterized by disease and symptom progression despite maximally-tolerated goal-directed therapy.[1] Such patients are frequently admitted for decompensation and are at high risk of death during and after HF hospitalization.[2] Cardiac transplantation and durable mechanical circulatory support can markedly improve quality and length of life in advanced HF, but appropriate patient selection remains challenging.[3] Patients near the end of life who are not candidates for or do not desire such aggressive interventions may derive substantial benefit from hospice referral, but predicting 6-month mortality in advanced HF can be difficult. [2,4]

The well-described 'obesity paradox' links higher body mass index (BMI) with lower short- and long-term mortality in HF; conversely, HF patients with low BMI have poorer survival.[5,6] Cardiac cachexia, a catabolic wasting state associated with inflammation and neurohormonal activation, is generally believed to mediate poor outcomes in HF patients with low BMI or weight loss. However, while often overlooked, poor nutritional status is also an important prognostic factor. Low serum albumin strongly predicts mortality across the spectrum of HF severity from ambulatory patients to left ventricular assist device (LVAD) recipients.[7,8]. Detailed assessments including anthropometric and survey measures indicate that the HF obesity paradox is substantially modulated by nutritional status and that in turn, BMI is not a good predictor of nutritional status in HF.[9-11]

The Nutritional Risk Index (NRI), an easily calculated measure that incorporates albumin and body size, predicts mortality in single-center cohorts of ambulatory [12] and hospitalized [13] HF patients. The impact of NRI on mortality risk in advanced HF is unknown. We analyzed data from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) study. In this well-characterized HF inpatient cohort, a bedside mortality risk prediction score (ESCAPE model) with good discrimination has previously been developed.[14] We hypothesized that the NRI would improve risk stratification for 6-month mortality at hospital discharge in the ESCAPE study cohort, particularly in the patients at highest risk of death.

Methods

The ESCAPE trial enrolled patients from 26 academic centers in the U.S. and Canada with advanced HF/cardiac transplant programs. The design, endpoints, and results of the ESCAPE trial have been previously published.[2] In brief, the study randomized advanced HF inpatients to therapy guided by clinical assessment alone or clinical assessment plus pulmonary artery catheterization. All enrolled patients had New York Heart Association class IV symptoms despite therapy with angiotensin-converting enzyme inhibitors and diuretics, as well as one or more prior HF hospitalizations and/or substantial diuretic resistance during outpatient management. Other factors aimed at recruiting an advanced HF cohort included left ventricular ejection fraction ≤ 30%, presenting systolic blood pressure of ≤ 125 mmHg,[15] and clinical evidence of congestion.

Of the subjects enrolled in ESCAPE who were not lost to follow-up, 20% died and 65% died or were readmitted within 6 months, confirming that the cohort represented advanced HF. Noting substantial clinical differences between survivors and non-survivors, several investigators derived a risk model for 6-month post-discharge mortality. Based on Cox model coefficients, a simplified integer risk score (hereafter referred to as the ESCAPE model) was developed that assigned 1 point each for age > 70 years, BUN > 40 mg/dL and BUN > 90 mg/dL, 6-minute walk distance < 300 feet, serum sodium < 130 mEq/L, daily diuretic dose at discharge > 240 mg furosemide equivalent, absence of beta-blocker at discharge, and discharge BNP > 500 pg/mmol, 2 points for cardiac arrest or mechanical ventilation during the index hospitalization, and 3 points for discharge BNP > 1300 pg/mmol. In the ESCAPE cohort, overall discrimination was good and 6-month mortality increased in stepwise fashion with this integer score. [14]

The Nutritional Risk Index (NRI) was calculated as NRI = (1.519 × serum albumin, g/dL) + [41.7 × weight (kg)/ideal body weight (IBW; kg)]. The IBW was calculated with the Devine formula for men (IBW [kg] = 50 kg + 2.3 kg for each inch of height > 5 feet) and the Robinson formula for women (IBW [kg] = 48.67 kg +1.65 kg for each inch of height > 5 feet).[16] .As in other previous studies, in patients with discharge weight greater than IBW, we set this ratio = 1.[17,18] Typically, NRI ≥ 100 indicates no evidence of malnourishment, 97.5 to 100 indicates mild, 83.5 to 97.5 moderate, and < 83.5 severe risk of malnourishment-related complications. Given the expectation that many ESCAPE patients were volume-overloaded at hospital admission and additionally that the ESCAPE model uses discharge data, we used albumin and body weight data at the time of hospital discharge to calculate NRI. In the ESCAPE patients assigned to pulmonary artery catheter monitoring, we explored the relationship between NRI, serum albumin, and hemodynamic factors.

We calculated the ESCAPE model integer score in patients who were not lost to follow-up and the NRI in all patients with complete data. We used Cox proportional hazard modeling to evaluate the primary outcome of all-cause mortality over 6 months of follow-up, first for the ESCAPE model and the NRI alone, then in combination. We then evaluated for differential efficacy of NRI in high- and low-risk ESCAPE patients with log-rank testing, creating four subgroups dichotomized at an NRI value of 100 and a predicted 6-month mortality risk of 20% (corresponding to an ESCAPE model integer score ≥ 2). We reviewed the performance of the model after excluding patients who underwent transplant and/or LVAD placement within 6 months. We performed a sensitivity analysis adjusting for changes in serum hemoglobin during hospitalization, as hemoconcentration may affect both discharge weight and albumin values.

Results

Baseline characteristics of the 160 patients with calculated NRI and the remaining 254 ESCAPE study patients are shown in *Table 1*. The NRI group was slightly younger, but otherwise nearly identical to the remainder of the ESCAPE cohort. In addition to clinical characteristics, the observed 6-month mortality and incidence of transplant or LVAD placement were very similar between groups.

Across the entire ESCAPE cohort, 82 of 414 (20%) patients died within six months; 30 of 160 (19%) patients died in the NRI group. The ESCAPE risk model retained good discrimination in the NRI cohort, with c-statistic 0.74 and a stepwise increase in mortality hazard with increasing integer score. On a univariable basis, increasing NRI score showed a strong trend towards lower mortality hazard (HR 0.67, 95% CI 0.44-1.02, p = 0.06). With respect to individual components of the NRI, there was no significant change in albumin (admission 3.7±0.5 vs. discharge 3.7±0.5 g/dL, p = 0.85 by paired t-testing) but weight decreased between hospital admission and discharge (86.5±22 to 82.8±21 kg, p < .001 by paired t-testing).

When added to the ESCAPE model, NRI predicted 6-month mortality independent of the ESCAPE integer score (p = 0.02) and the c-statistic of the overall model increased (*Table 2*). Results were identical when the 17 NRI cohort patients who underwent cardiac transplantation or LVAD implantation within 6 months were excluded from the analysis (adjusted HR 0.60 [95% CI 0.37-0.96] per 10 units NRI, p = 0.03). As in other studies, we defined at-risk for nutrition-related complications as an NRI < 100.[13,18] The *Figure* demonstrates that at-risk status by the NRI was particularly effective in further risk-stratifying the subset of patients with high baseline predicted mortality by the ESCAPE model (≥ 20%, corresponding to an ESCAPE model score ≥ 2), with little effect in lower-risk patients. In this high-risk cohort, 6-month mortality in patients with NRI > 100 was 14% and in those with NRI < 100 was 38%.

In the 78 ESCAPE patients with NRI and invasive hemodynamic data, the serum albumin and NRI did not significantly correlate with right atrial pressure, pulmonary artery pressures, pulmonary capillary wedge pressure, cardiac index, or right ventricular stroke work index at baseline or at the end of pulmonary catheter monitoring. In the NRI cohort there were no significant differences between low vs. high-risk ESCAPE score patients in discharge albumin, weight, or BMI values (albumin: 3.7±0.6 vs. 3.6±0.5 g/L, p=0.48; weight 84±22 vs. 82±20 kg, p=0.44; BMI: 28±7 vs. 27±6 kg/m2, p=0.21).

The BMI (at admission or discharge), admission albumin level, and NRI calculated at hospital admission did not significantly predict 6-month mortality on a univariable or adjusted basis. We performed additional sensitivity analyses to clarify which factors mediated the effect of discharge NRI. We hypothesized that associations with discharge but not admission NRI could relate to hemoconcentration following diuresis, previously associated with improved outcomes in acute decompensated heart failure.[19] However, when we adjusted for change in hemoglobin during hospitalization and the ESCAPE risk score in the 149 patients with complete data, we observed similar effect size for discharge NRI (HR 0.61, 95% CI 0.37-1.01, p=0.056). Most (77%) ESCAPE patients had discharge weight greater than IBW, reducing the sensitivity of the NRI to body weight and making it more dependent on albumin. We recalculated the NRI using the true discharge weight:IBW ratio in all patients (i.e. allowing the ratio to be > 1). The NRI was no longer independently predictive as a continuous variable (adjusted HR 0.89, 95% CI 0.69-1.14, p=0.35). However, an NRI < 100 (i.e. at-risk nutritional status) remained helpful in risk-stratifying patients, with log-rank test for trend p<0.001 across categories (ESCAPE risk score and NRI dichotomized at 2 and 100 respectively as in the *Figure*). Again the NRI tended to be most

helpful in patients with ESCAPE risk score ≥ 2 (6-month mortality in such patients with NRI > 100 was 24% and in those with NRI < 100 was 41%, p=0.12).

Discussion

In this study we demonstrate that the hospital discharge NRI independently predicts 6 month mortality in advanced HF inpatients. The NRI was particularly useful in the subset of advanced HF patients who already had high predicted risk of death.

The obesity 'paradox' in HF has been extensively documented, with higher BMI appearing protective and low BMI harmful in both chronic and acute HF. [6,20,21] This issue has not been extensively studied in advanced HF inpatients, and interestingly BMI had no relationship with mortality in the ESCAPE cohort. In HF patients, BMI does not always correlate well with nutritional status, [10] an often underappreciated risk factor. Aggarwal and colleagues investigated nutritional status in 154 advanced HF patients undergoing evaluation for LVAD or cardiac transplant. Using the Mini Nutritional Assessment, they observed that undernourishment independently predicted all-cause mortality (OR 7.9, 95% CI 1.01–62.30; P = .04) after adjusting for albumin and hemoglobin. [22] However, the Mini Nutritional Assessment contains 18 items and requires accurate anthropometric measurements (arm and calf circumference), and in the Aggarwal study nearly 90% of patients were flagged as undernourished. The ease of implementation and practical utility of the Mini Nutritional Assessment on a broader basis in advanced HF are thus uncertain.

In observational studies and clinical trial cohorts, relatively modest weight loss of 5-6% or more strongly predicts worsened survival in HF patients. [5,23,24] Unintentional weight loss in HF is often attributed to cardiac cachexia, a dysregulated state of imbalance between catabolism and anabolism. Cachexia has multiple contributing factors including poor nutrition, [25,26] and usually involves loss of muscle mass and fat. The diagnostic criteria for cachexia include: ≥ 5% weight loss over ≤ 12 months in the presence of underlying illness, plus three of the following: decreased muscle strength, fatigue, anorexia, low fat-free mass index, or abnormal biochemistry (including increased C-reactive protein > 5.0 mg/dl, IL-6 > 4.0 pg/ml, anemia, or low albumin < 3.2 mg/dl). [27]

The NRI touches on two key components of cachexia as defined above, and may be an appropriate screening evaluation in advanced HF – particularly since (in contrast to previous work in less ill HF patients [28,29]) BMI and admission albumin level as individual factors were not predictive in the ESCAPE study cohort. Since cachexia is associated with poor outcomes and may be challenging to reverse, it is likely important to recognize HF patients at risk prior to reaching this stage. In our study, even mild-to-moderate nutritional risk by NRI score substantially increased 6-month mortality in the specific subset of patients who might be considered for advanced HF therapies.

Beyond mortality prediction, NRI or other nutritional risk assessment would have greater utility if proven interventions in HF were defined. Specific approaches to cardiac cachexia are under study, but are largely still in the pre-clinical stage.[30-34] Surprisingly few nutritional intervention trials have been performed in patients with cachexia related to

chronic illness,[35] particularly in advanced HF. A small Russian study demonstrated increases in lean body mass and 6-minute walk distance in patients with New York Heart Association class III-IV HF following 24 weeks of enteric nutritional supplementation,[36] and the use of enteral and parenteral nutritional support in the perioperative setting for left ventricular assist device implantation is increasing.[37] It is worth noting that restrictive diets, including those recommending low sodium intake, increase the risk of undernutrition in the elderly.[38] An important opportunity exists to study whether dietary education or direct nutritional supplementation, with or without pharmacological intervention, could improve prognosis or delay progression to cardiac cachexia in advanced HF.

Limitations

We were only able to calculate NRI in those ESCAPE cohort patients who had discharge serum albumin levels measured, although the characteristics of this group were nearly identical to the ESCAPE study population as a whole (see *Table 1*). Hemodynamic data were not available for all patients, but in the ESCAPE subset randomized to pulmonary artery catheterization there appeared to be no relationship between the NRI and hemodynamic information. The NRI is not a comprehensive assessment of nutritional intake, anabolic/catabolic balance, or specific nutrient requirements and provides only a snapshot of risk. However, its simplicity makes it attractive as a screening tool, which could then be followed by more labor-intensive and patient-specific evaluation in appropriate circumstances.

Conclusions

The NRI, developed to evaluate risk for nutrition-related complications, improves 6-month mortality risk prediction in advanced HF patients at high risk of death. This simple and easily obtained parameter might help identify HF patients who require evaluation for advanced HF therapies or additional palliative interventions.

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Abbreviations

BMI	body mass index
BNP	B-type natriuretic peptide
BUN	blood urea nitrogen
ESCAPE	Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness
HF	heart failure
IBW	ideal body weight

NRI nutritional risk index

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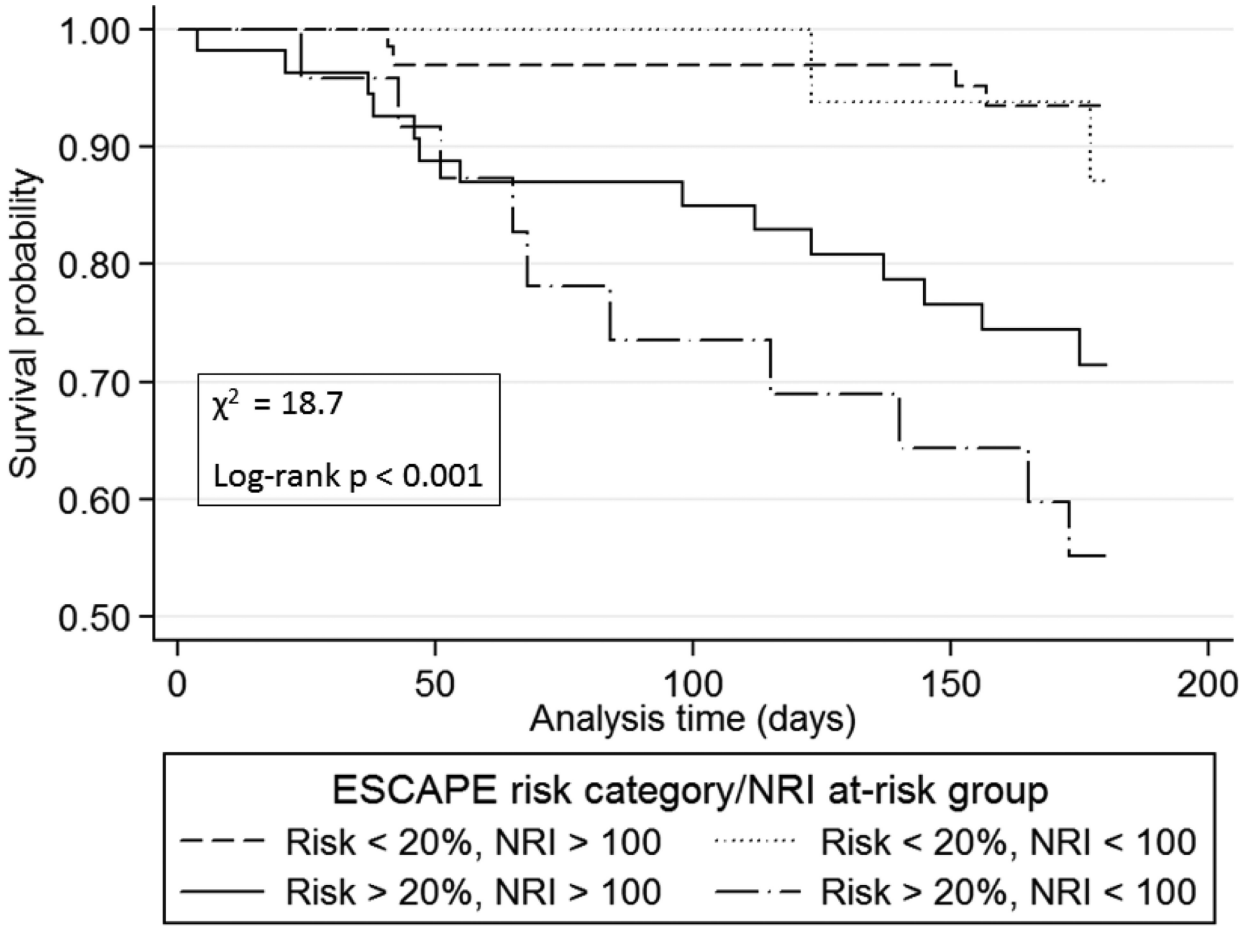

Figure. Relationship between predicted mortality risk and NRI

Abbreviations: ESCAPE: Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness; NRI: nutritional risk index

Table 1

Baseline characteristics

Variables	NRI cohort (n = 160)	Other patients (n = 254)
Age (years)	54±13	58±14*
Gender (female)	23%	28%
Race (Caucasian)	63%	59%
Body mass index (kg/m^2)	29±7	29±7
Length of stay (days)	8±6	9±7
Ischemic etiology	48%	52%
History of:		
Hypertension	46%	48%
Diabetes mellitus	31%	32%
COPD	18%	17%
Heart rate (beats/min)	82±16	82±15
Systolic blood pressure (mmHg)	103±15	106±17
Serum sodium (mEq/L)	137±4	137±5
Blood urea nitrogen (mg/dL)	34±19	36±24
Serum creatinine (mg/dL)	1.5±0.6	1.5±0.6
BNP (pg/mmol)	950±110	1037±96
Transplant/LVAD within 6 months	11%	9%
Observed 6-month mortality	19%	20%

Abbreviations: BNP, B-type natriuretic peptide; COPD, chronic obstructive pulmonary disease; ESCAPE, Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness; LVAD, left ventricular assist device; NRI, nutritional risk index

$p < .05$ for comparison between groups

Table 2

ESCAPE model, NRI, and 6-month mortality in NRI cohort

Variables	ESCAPE model	ESCAPE model + NRI
ESCAPE model points		
0	(reference)	(reference)
1	0.43 (0.08-2.36)	0.47 (0.09-2.59)
2	2.84 (0.87-9.24)	2.83 (0.87-9.21)
3	2.65 (0.59-11.87)	2.34 (0.53-10.61)
4	2.90 (0.65-12.96)	2.83 (0.63-12.67)
5	4.56 (1.02-20.42)	6.57 (1.42-30.38)
6	3.73 (0.42-33.36)	3.22 (0.36-28.86)
7	7.05 (1.57-31.58)	7.04 (1.57-31.65)
≥8	34.06 (5.74-202.20)	64.30 (9.67-427.47)
NRI (per 10 units)		0.60 (0.39-0.93)
C-statistic	0.74	0.76

Abbreviations: ESCAPE, Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness; NRI, nutritional risk index