Prognostic nutritional index in elderly patients hospitalized for acute heart failure

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Abstract

Aims Acute heart failure (AHF) represents a frequent cause of hospitalization and is associated with significant mortality among elderly patients. Risk assessment models like the prognostic nutritional index (PNI) have been proposed to stratify the risk of death and identify patients requiring more intensive levels of care. We evaluated the predictive value of PNI for in-hospital and overall mortality in a cohort of consecutive elderly patients hospitalized for AHF.

Methods and results Prognostic nutritional index, laboratory, and clinical parameters were collected upon admission. PNI values were calculated from albumin concentration and lymphocyte count and reported on a continuous scale with lower values indicating worse prognosis. The primary outcome was overall all-cause mortality de

Conclusions Low PNI values are associated with short-term and long-term mortality among elderly patients hospitalized for acute decompensated heart failure. Future studies are warranted to confirm these findings and evaluate the use of PNI to guide therapeutic decisions.

Keywords Heart failure; Prognostic nutritional index

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Introduction

Acute heart failure (AHF) is a common cause of hospitalization among elderly patients with a prevalence that reaches about 10% in those 70 years or older.1 Despite its management has significantly improved over the past decades, AHF remains a major determinant of morbidity and mortality in elderly patients.1

Reduced mobility, poor functional and nutritional status, as well as cognitive impairment have been associated with higher mortality, but findings remain conflicting.2–5 The prognostic nutritional index (PNI), which is calculated from serum albumin concentration and lymphocyte count, was recently proposed as a tool to stratify mortality risk in patients with AHF.6 PNI was initially derived in a cohort of 200 patients with gastric cancer undergoing surgery in whom lower PNI values predicted worse prognosis.7 In a systematic review and meta-analysis, Sun and colleagues confirmed the predictive value of PNI for mortality and post-operative complications in different types of cancer.8 More recently, higher PNI has
been associated with long-term survival in patients with AHF.5,9 Both components of the PNI, albumin, and lymphocytes, may convey relevant and independent prognostic information in patients with AHF. Albumin concentrations are influenced by nutrition, renal and liver function, and inversely correlate with the severity of congestive heart failure.10 The lymphocytes count reflects the inflammatory and immune system activation, and low counts could indicate immune hypo-responsiveness and increased production of cortisol, which may negatively affect the clinical course of AHF.11 PNI can be easily calculated at patient bedside using routine laboratory parameters and is not influenced by operator judgement, offering a practical and affordable tool to stratify risk in elderly patients with AHF. However, PNI requires validation before it can be implemented in clinical practice.

The aim of the current study was to assess the predictive value of the PNI for in-hospital and overall mortality in a prospective cohort of elderly patients hospitalized for AHF.

Materials and methods

Study population

Prospective observational cohort study in elderly patients with chronic heart failure who were hospitalized because of an acute decompensation into our Geriatric Unit, Chieti, Italy from December 2016 to February 2018. AHF was diagnosed in the presence of typical signs and symptoms, laboratory test results, and, when available, echocardiographic findings of cardiac dysfunction.5 Exclusion criteria were age below 65 years, presence of sepsis, severe liver cirrhosis (Child–Pugh score B or C), and lack of informed consent. The primary outcome was overall all-cause mortality defined as death from any cause occurring during hospitalization up to 6 months after discharge. The secondary outcomes were in-hospital and post-discharge all-cause mortality.

The study was approved by the local institutional review board, and all patients provided informed consent before study procedures.

Data collection

We collected information on demographics, comorbidities (e.g. history of stroke/transient ischemic attack, chronic kidney disease, diabetes mellitus), physical examination (e.g. blood pressure), bedridden status for 1 month or longer, imaging performed during hospitalization (e.g. chest X-ray), concomitant medications, and routine laboratory measurements [e.g. blood count, renal and hepatic function, N-terminal brain natriuretic peptide (NT-proBNP)]. PNI was calculated upon admission according to the following formula: [10 × serum albumin (g/dL)] + (0.005 × total lymphocyte count/mm)3.6 The PNI values are reported on a continuous scale with lower values indicating worse prognosis.

A phone contact or visit was scheduled at 6 months after discharge to evaluate the occurrence of death or rehospitalization.

Statistical analysis

Continuous variables are reported as mean (standard deviation) and categorical variables as numbers (percentage). Differences were evaluated by the χ2 and Mann–Whitney tests, as appropriate. The association between PNI as continuous variable and mortality was evaluated calculating hazard ratios (HRs) and the relative 95% confidence intervals (CIs) by Cox proportional regression analysis. Variables considered in multivariable analysis for their potential association with mortality included age, sex, levels of NT-proBNP, anaemia, and bedridden status.12,13 NT-proBNP presented a skewed distribution and values were log-transformed before analysis. According to the World Health Organization (WHO), anaemia was defined as haemoglobin (Hb) levels <12.0 g/dL in women and <13.0 g/dL in men.

We applied the Youden’s index to calculate the optimal PNI cut-off for the prediction of mortality. This value was used to stratify the study population in two groups (i.e. low and high PNI), and its predictive value was assessed in Cox regression analysis. Kaplan–Meier survival curves were generated for overall all-cause mortality and verified with log-rank test. Participants were censored at the end of the follow-up period.

All analyses were conducted using using R statistic 3.4.3 (2017-11-30).

Results

The study population included 344 patients with a median age of 84 years (range 65 to 101). Fifty-eight patients (16.9%) were NYHA II, 188 (54.7%) NYHA III, and 98 (28.5%) NYHA IV.

Median PNI was 34 (range 17 to 55). Patients with PNI below the median (n = 189, 54.9%) were older, more often bedridden, had higher levels of NT-proBNP (14 606 pg/mL vs. 8099 pg/mL, P = 0.001), and lower lymphocytes (1.28 × 109/L vs. 1.52 × 109/L, P = 0.008) and albumin (3.22 g/dL vs. 3.59 g/dL, P ≤ 0.001) compared with patients with PNI above the median (n = 155, 45%). The average duration of hospitalization was 8 days (range 1 to 30) in patients with high PNI vs. 10 days (range 1 to 17) in those with low PNI. Baseline characteristics of the study population according to PNI values are presented in Table 1.

A total of 115 (33.4%) patients were rehospitalized during a median follow-up of 158 days (range 2 to 180 days), most
commonly because of heart failure (n = 73, 21.2%). In the group with low PNI, 66 (34.9%) patients were rehospitalized, and the reason for admission was recurrent AHF in 43 (22.8%). The corresponding figures in the group of patients with PNI above 34 were 49 (31.6%) and 30 (19.4%), respectively.

**Prognostic nutritional index and mortality**

Twenty-eight patients (8.1%) died during hospitalization and 47 (13.7%) died after discharge for an overall mortality rate of 21.8%. The most frequent cause of death was cardiovascular disease, which accounted for 41% of cases.

In univariable analysis, the PNI values were inversely associated with the risk of overall mortality (HR 0.90; 95% CI, 0.87 to 0.94), in-hospital mortality (HR 0.91; 95% CI, 0.85 to 0.98), and post-discharge mortality (HR 0.92; 95% CI, 0.87 to 0.97; Table 2). After adjusting for age, sex, bedridden status, anemia, and NT-proBNP in multivariable analysis, PNI remained associated with overall mortality (HR 0.93; 95% CI, 0.89 to 0.98) and post-discharge mortality (HR 0.94; 95% CI, 0.89 to 1.00), while the association with in-hospital mortality was no longer statistically significant (HR 0.95; 95% CI, 0.88 to 1.02). Additional predictors of overall all-cause mortality were age (HR 1.06; 95% CI, 1.02 to 1.10), bedridden status (HR 2.23; 95% CI, 1.37 to 3.62), and NT-proBNP (HR 1.25; 95% CI, 1.04 to 1.53). The presence of anemia was not an independent predictor of death (HR 1.13; 95% CI, 0.72 to 1.79).

The Youden’s index found that the optimal PNI value to predict mortality risk was 34 which was used to stratify the study population in a group with low PNI (i.e. ≤34) and a group with high PNI (i.e. >34). Patients with PNI values ≤34 had significantly higher mortality compared with patients

### Table 1 Baseline characteristics of study population at admission

|                        | Total population | Low PNI (≤34) | High PNI (>34) | P test |
|------------------------|------------------|---------------|----------------|--------|
| N                      | 344              | 189           | 155            |        |
| Age, mean (SD)         | 83.56 (7.15)     | 84.43 (7.32)  | 82.49 (6.81)   | 0.012  |
| Sex, female, n (%)     | 186 (54.1)       | 104 (55.0)    | 82 (52.9)      | 0.776  |
| NYHA class, n (%)      |                  |               |                | 0.048  |
| III                    | 188 (54.7)       | 100 (52.9)    | 88 (56.8)      |        |
| IV                     | 98 (28.5)        | 63 (33.3)     | 35 (22.6)      |        |
| Cardiopathy, n (%)     |                  |               |                |        |
| Ischemic               | 104 (30.2)       | 65 (34.4)     | 39 (25.2)      | 0.082  |
| Not ischemic           | 240 (69.8)       | 124 (65.6)    | 116 (74.8)     |        |
| Comorbidities at admission, n (%) |        |               |                |        |
| Bedridden              | 79 (23.0)        | 55 (29.1)     | 24 (15.5)      | 0.004  |
| Atrial fibrillation    | 177 (51.5)       | 95 (50.3)     | 82 (52.9)      | 0.705  |
| Diabetes               | 116 (33.7)       | 66 (34.9)     | 50 (32.3)      | 0.685  |
| Hypertension           | 264 (76.7)       | 137 (72.5)    | 127 (81.9)     | 0.053  |
| COPD                   | 110 (32.0)       | 64 (33.9)     | 46 (29.7)      | 0.477  |
| Chronic kidney disease | 124 (36.0)       | 71 (37.6)     | 53 (34.2)      | 0.592  |
| Anaemia                | 139 (40.4)       | 89 (47.1)     | 50 (32.3)      | 0.007  |
| Laboratory Exams, mean (SD) |            |               |                |        |
| Haemoglobin, g/dL      | 11.69 (2.15)     | 11.30 (2.11)  | 12.16 (2.12)   | <0.001 |
| Leukocytes, ×10^3/μL   | 38.48 (539.27)   | 10.05 (5.11)  | 73.15 (803.42) | 0.281  |
| Lymphocytes, ×10^3/μL  | 1.39 (0.82)      | 1.28 (0.70)   | 1.52 (0.94)    | 0.008  |
| Albumin, g/dL          | 3.39 (0.57)      | 3.22 (0.55)   | 3.59 (0.54)    | <0.001 |
| NT-proBNP, pg/mL       | 11,674 (17406)   | 14,606 (19381) | 8,099 (13888) | 0.001  |
| Creatinine, mg/dL      | 1.34 (0.72)      | 1.40 (0.82)   | 1.27 (0.57)    | 0.112  |
| Therapy at admission, n (%) |        |               |                |        |
| ACE inhibitors         | 95 (27.6)        | 49 (25.9)     | 46 (29.7)      | 0.514  |
| ARB blocker            | 49 (14.2)        | 22 (11.6)     | 27 (17.4)      | 0.170  |
| Beta blocker           | 188 (54.7)       | 98 (51.9)     | 90 (58.1)      | 0.297  |
| Loop diuretics         | 265 (77.0)       | 146 (77.2)    | 119 (76.8)     | 1.000  |
| Aldosterone antagonist | 126 (36.6)       | 72 (38.1)     | 54 (34.8)      | 0.609  |
| Antiplatelet agent     | 149 (43.3)       | 86 (45.5)     | 63 (40.6)      | 0.426  |
| Anticoagulant          | 134 (39.0)       | 65 (34.9)     | 69 (44.5)      | 0.071  |

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; NT-proBNP, N-terminal pro-brain natriuretic peptide; SD, standard deviation.

### Table 2 Cox regression analysis for prognostic nutritional index and mortality

|                        | HR crude (CI 95%) | HR adjusted* (CI 95%) | P value |
|------------------------|-------------------|-----------------------|---------|
| In-hospital mortality  | 0.91 (0.85 to 0.98)| 0.95 (0.88 to 1.02)   | 0.17    |
| After discharge mortality | 0.92 (0.87 to 0.97)| 0.94 (0.89 to 1.00)   | 0.05    |
| Overall mortality      | 0.90 (0.87 to 0.94)| 0.93 (0.89 to 0.98)   | 0.002   |

CI, confidence interval; HR, hazard ratio.

*Adjusted for age, sex, bedridden, anaemia, and NT-proBNP.
with high PNI (Figure 1). Fifty-five patients (29.1%) with low PNI died during follow-up compared with 20 (12.9%) with high PNI (HR 2.54; 95% CI, 1.52 to 4.24). The corresponding figures were, respectively, 24 (12.7%) vs. 4 (2.6%) for in-hospital mortality (HR 3.37; 95% CI, 1.14 to 9.95), and 31 (16.4%) vs. 16 (10.3%) for post-discharge mortality (HR 1.88; 95% CI, 1.03 to 3.44).

The time course of overall mortality in patients with low and high PNI values is shown in Figure 2.

Discussion

In the current study, low PNI was associated with a higher risk of overall mortality in elderly patients admitted for AHF, independently of age, sex, bedridden status, anaemia, and NT-proBNP levels.

In a retrospective study of 119 patients with acute decompensated heart failure, low serum albumin predicted worse survival, and in a cohort of 211 elderly patients with advanced heart failure, low lymphocyte concentrations were associated with higher mortality. Recently, two studies evaluated the prognostic value of the combination of serum albumin and lymphocyte count in patients with heart failure. In a prospective cohort of 285 outpatients with heart failure and preserved ejection fraction, Agus and colleagues found that PNI values below 37 were able to predict higher all-cause mortality and rehospitalization at 1 year. This study included a relatively young (mean age of 68 years) group of ambulatory patients with lower mortality rate compared with that observed in patients hospitalized for AHF. In a retrospective analysis of the Heart Failure Registry of Taipei Veterans General Hospital, low PNI was associated with higher short-term and long-term all-cause mortality among 1673 inpatients (mean age 76 years) admitted for AHF. Our results provide prospective validation of these findings and confirm the role of PNI for the prediction of all-cause mortality in an older population hospitalized for AHF.

The predictive value of PNI is likely explained by the close relationship of serum albumin and lymphocyte count with a number of negative prognostic factors. Low lymphocytes count could indicate lower immune system activity with increased patient vulnerability to pathological noxae. In addition, lower lymphocytes may be the result of increased cortisol levels, which could have a negative impact on AHF prognosis. Low serum albumin concentrations may be a marker of renal and liver dysfunction or poor nutritional status. In elderly patients with heart failure, several other factors may influence serum albumin levels including ageing itself or changes in body water distribution. The close relationship of both PNI components with multiple comorbid
conditions may explain the higher PNI values in previous cohorts of ambulatory and clinically stable patients with heart failure compared with the PNI values found in the current study population.6,9

The strengths of the study include the prospective design, no losses to follow-up, and the inclusion of a study population which was relatively older compared with those evaluated in earlier studies.

The current study has some limitations which need to be acknowledged. First, this was a single centre study on patients hospitalized in a Geriatric unit, and results may not be generalizable to other settings. For example, the definition of low PNI may differ between hospitalized patients with AHF and outpatients with chronic heart failure. When we used PNI thresholds of 37 or PNI tertiles as evaluated in earlier studies on relatively younger populations, there was no significant association between PNI and mortality (data not shown). Second, the size of the study was relatively small, and validation of current findings in larger study populations is warranted. Third, potential significant predictors like ejection fraction were not systematically collected leaving the potential for residual confounding. Fourth, a multidimensional geriatric assessment was not available in all patients which precluded the possibility to correct for geriatric status in the analysis.Interestingly, the presence of a bedridden condition since at least 1 month before admission was a significant marker of poor prognosis. Bedridden status in elderly patients is considered as a clinical geriatric syndrome which is associated with disability, increased susceptibility to adverse events, and higher mortality. Bedridden status together with low PNI identified a group of patients with worse prognosis who may be the target of higher intensity of care, rehabilitation, or longer monitoring to improve recovery. Finally, this study considered a 6-month follow-up after discharge; thus, the predictive value of PNI over longer time periods remains unclear. However, the calculation of PNI is based on laboratory parameters which may change over time, and this could potentially reduce the usefulness of the tool during long-term follow-up. The value of repeated assessment of PNI after 6 months requires further study.

Conclusions
Low PNI values predict short-term and long-term all-cause mortality among elderly patients hospitalized for acute decompensated heart failure. Additional studies are warranted to validate these findings and explore the potential use of PNI to guide therapeutic decisions.

Conflict of interest
Candeloro M, Balducci M, Genova S, Valeriani E, Pierdomenico S, and Porreca E have no relevant conflicts to declare. Di Nisio M received personal fees from Bayer, Daiichi Sankyo, Pfizer, and Leo Pharma outside the submitted work.

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Author contribution
Study conception and design: Candeloro M, Di Nisio M, Porreca E; Data acquisition: Candeloro M, Balducci M, Genova S; Statistical analysis: Candeloro M, Di Nisio M; Interpretation of the data: All authors; Drafting, critical revision, and final approval of the manuscript: All authors.

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