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Original Research

# Naples Prognostic Score and Clinical Outcomes in Pulmonary Arterial Hypertension Patients

**Emre Arugaslan, Suleyman Kalayci, Omac Tufekcioglu**

**Department of Cardiology, Ankara City Hospital, Ankara, Türkiye**

## ABSTRACT

**Objectives:** Pulmonary arterial hypertension (PAH) is a specific form of pulmonary hypertension characterized by an increased mean pulmonary arterial pressure. Risk stratification is crucial in managing PAH, using various clinical, laboratory, and imaging parameters. The Naples prognostic score (NPS), incorporating nutritional and inflammatory markers, has demonstrated prognostic value in other conditions but not in PAH. The goal of this study was to appraise the importance of NPS as a prognostic indicator for patients with PAH.

**Methods:** This retrospective study involved 101 PAH patients. Echocardiographic, laboratory, and right heart catheterization data were collected. Statistical analyses compared variables between survivors and non-survivors, and multivariate logistic regression identified mortality risk factors.

**Results:** Among the 101 patients, 18 died within the follow-up period. The mortality group showed elevated levels of B-type natriuretic peptide (BNP) and significantly higher median NPS. Patients were categorized based on their NPS scores, revealing higher mortality in Group 2. Multivariate logistic regression identified age and BNP levels as independent predictors of mortality. The inclusion of NPS in the model further reinforced its association with mortality.

**Conclusion:** The study suggests that NPS is linked to poor outcomes in PAH patients. NPS, a straightforward and easily calculated score, holds the potential to predict the clinical trajectory of PAH, offering advantages for risk assessment in this population.

**Keywords:** B-type natriuretic peptide, Monocyte-to-lymphocyte ratio, Naples prognostic score, Neutrophil-to-lymphocyte ratio, Pulmonary arterial hypertension

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Pulmonary hypertension is defined as a mean pulmonary arterial pressure higher than 20 mmHg at rest.[1] Pulmonary arterial hypertension (PAH) is a subtype of pulmonary hypertension, with a prevalence of 48–55 cases per million adults.[2] The long-term mortality rate was 12.9% in a recent registry.[3]

Risk stratification is an important part of the management of patients with PAH. It is recommended to evaluate the disease's severity using a data panel derived from clinical assessment, 6-min walking distance (6MWD), B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) levels, imaging, and hemodynamic findings.[4] In addition, nutritional status was associated with prognosis in patients with primary pulmonary hypertension.[5]

Inflammation is thought to contribute to pulmonary vascular disease, and some inflammatory cytokines had prognostic value in PAH.[6,7] Furthermore, inflammation has been identified as a key driver for disease-related malnutrition.[8]

**Address for correspondence:** Emre Arugaslan, MD. Department of Cardiology, Ankara City Hospital, Ankara, Türkiye
**Phone:** +90 530 975 07 49 **E-mail:** dremrearugaslan@gmail.com

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PAH-specific drugs are designed to target the underlying mechanism of the condition.[1] These drugs can be tailored according to the clinical assessment of the patients. An easy and applicable risk assessment tool can provide valuable information in drug selection, prevent unnecessary treatment, and most importantly help in the selection of patients who need early and aggressive treatment.

The Naples prognostic score (NPS) has gained recognition as a precious prognostic tool for colorectal cancer patients.[9] It includes serum albumin, total cholesterol, neutrophil-to-lymphocyte ratio (NLR), and lymphocyte-to-monocyte ratio (LMR) levels and reflects the patients' inflammatory and nutritional status. This score has recently been associated with worse outcomes in patients with acute coronary syndrome and heart failure (HF).[10-13] However, the role of the NPS score in PAH has not yet been studied. We aimed to assess the prognostic impact of NPS in patients with PAH.

## Methods

### Study Population

This retrospective and observational study included 101 patients with PAH who presented to Ankara City Hospital between May 2019 and April 2023. Patients with advanced liver and kidney disease, active infection, missing laboratory parameters, statin therapy, terminal malignancy, malnutrition, and the pediatric age group were excluded from the study. Our study was endorsed by the Local Ethics Board of our institute (Date: May 10, 2023, Decision No: E1-23-3553) and followed the principles set out in the Declaration of Helsinki for human investigations. Echocardiographic, laboratory, and right heart catheterization (RHC) parameters were obtained from patient records. The definition of PAH is based on hemodynamic assessment by RHC. PAH patients include Group 1 pulmonary hypertension defined in the most recent guideline.[1] NPS was calculated as previously described in the literature.[9]

### Statistical Analysis

Statistical analyses were carried out using IBM SPSS Statistics for Windows, Version 25.0 (Armonk, NY: IBM Corp). The distribution of data was assessed using the Shapiro–Wilk test. Continuous variables were presented as either the mean±standard deviation or the median (minimum-maximum), while categorical variables were expressed as frequency and percentage. Mean differences between groups were compared using the Student's t-test for normally distributed data, and the Mann–Whitney U-test was used for non-normally distributed data. Comparisons between groups for categorical data were made using the continuity-corrected Chi-square statistic of Pearson's Chi-square test. To evaluate differences among more than two groups, either the One-way analysis of variance or the Kruskal–Wallis test was used. Hence, we used the Kruskal–Wallis test to the analysis of the relationships between all-cause mortality and hospitalization according to Naples Group 0–2. Troponin, sex, C-reactive protein (CRP), total protein, urea, uric acid, age, BNP, and Naples score were used in multivariate logistic regression analysis with the backward elimination method to determine risk based on mortality by the models. For comparisons of model performance, −2 log-likelihood, Nagelkarke $R^2$, and Brier-scale score were calculated. $p<0.05$ was considered statistically significant for all tests.

## Results

A total of 101 patients with primary pulmonary hypertension were included in this study. The median follow-up period was 44 months. Demographics, clinic, and laboratory findings according to survival are presented in Table 1. The overall mortality rate was 17.8% (18–101 patients). The patients were similar in age, gender, and pulmonary artery pressure values. As expected, BNP levels were significantly higher in the mortality group (3493 ng/L vs. 297 ng/L, $p<0.001$). Total protein and albumin levels were lower in patients with mortality ($p=0.004$ and 0.038, respectively). In addition, NLR was higher and LMR was lower in the mortality group ($p<0.001$). The median NPS was 2 in the mortality group, whereas 1 in the survival group ($p=0.038$). The ROC curve analysis was performed to detect the cut-off values of NPS to predict mortality. For the cutoff value of NPS>2, the specificity was 87.95% and the sensitivity was 38.89% (AUC: 0.649, $p=0.060$).

The study population was allocated into three groups by NPS; NPS=0 indicates "Group 0," NPS=1–2 indicates "Group 1," and NPS=3–4 indicates "Group 2" (Table 2). Hereby, while the patients in Group 2 showed higher mortality rates, no significant difference was observed between the groups about hospitalization ($p=0.023$ and 0.071, respectively). A clustered column graph was used to illustrate this relationship on the Naples group's ground (Fig. 1).

The variables of troponin, sex, CRP, total protein, urea, uric acid, age, and BNP were used in multivariate logistic regression analysis with the backward elimination method to determine risk according to mortality in Model 1 (Table 3). Age and BNP levels were found to be independent predictors of mortality. When we added the Naples score to Model 1, BNP and Naples score were associated with mortality in Model 2. The comparison of model performances is shown in Table 4.

**Table 1.** Demographics, clinic, and laboratory findings according to survival

| Variables | Survival (n=83) | No-survival (n=18) | p |
|---|---|---|---|
| Age | 43.1±15 | 50±21 | 0.236 |
| Sex, female, n (%) | 55 (66) | 12 (66) | 1.000 |
| CHF | 4 (4.8) | 3 (16.7) | 0.056 |
| LVEF | 60 (30–76) | 60 (25–76) | 0.232 |
| Troponin | 10 (3–628) | 24 (5–155) | **0.044** |
| BNP | 297 (10–15757) | 3493 (118–14256) | **<0.001** |
| Glucose | 91 (62–156) | 92.5 (65–184) | 0.374 |
| HbA1C | 5.65 (5–9) | 6.05 (6–9) | 0.052 |
| AST | 22 (10–176) | 24 (16–1230) | 0.191 |
| ALT | 21 (10–130) | 19 (10–667) | 0.845 |
| CRP | 0.003 (0.0–0.31) | 0.01 (0.0–0.05) | **0.003** |
| Urea | 31±10 | 59±43 | **<0.001** |
| Creatinine | 0.77 (0.43–1.52) | 0.81 (0.52–4.01) | 0.062 |
| Uric acid | 6.5±4.9 | 7.4±2 | **0.004** |
| GFR | 101±21 | 84±31 | **0.038** |
| Total protein | 69±5.9 | 64.3±8.9 | **0.004** |
| Albumin | 43±4.4 | 40.4±5.2 | **0.038** |
| Total cholesterol | 166±40 | 143±40 | **0.036** |
| LDL | 96±30 | 82±27 | 0.081 |
| HDL | 44±10 | 38±14 | 0.066 |
| Triglyceride | 129±71 | 114±53 | 0.489 |
| TSH | 2.38±1.54 | 3.5±3.4 | 0.095 |
| WBC | 7.1±2.2 | 7.4±2 | 0.601 |
| NE | 4.4±1.8 | 5.3±1.8 | 0.070 |
| NE % | 62±9.6 | 70±8.4 | **0.001** |
| LY | 1.89±0.7 | 1.36±0.58 | **0.009** |
| LY % | 27±8.1 | 18.8±8.4 | **<0.001** |
| NLR | 2.29 (0.6–17.78) | 4.02 (1.25–14.41) | **<0.001** |
| Monocyte | 0.42±0.15 | 0.51±0.18 | 0.055 |
| LMR | 4.81±2.13 | 3.03±1.86 | **<0.001** |
| Hg | 14.8±3.2 | 13.1±2.8 | 0.075 |
| HTC | 45±10 | 41±9.1 | 0.111 |
| RDW | 14.9 (12–42.9) | 15.3 (13–22.8) | 0.136 |
| PLT | 215 (57–433) | 222 (95–592) | 0.445 |
| MPV | 8.4 (6.2–16.9) | 8.1 (6.9–13.4) | 0.370 |
| PCT | 0.19 (0.07–0.33) | 0.18 (0.11–0.51) | 0.477 |
| PDW | 53±14 | 54±10 | 0.884 |
| SPAP | 80±24 | 75±22 | 0.410 |
| MPAP | 52±18 | 47±20 | 0.431 |
| NAPLES score | 1 (0–4) | 2 (0–4) | **0.038** |

CHF: Congestive heart failure; LVEF: Left ventricular ejection fraction; BNP: B-type natriuretic peptide; CRP: C-reactive protein; WBC: White blood count; NLR: Neutrophil-lymphocyte ratio; LMR: Lymphocyte-monocyte ratio; SPAP: Systolic pulmonary artery pressure; MPAP: Mean pulmonary artery pressure.

**Table 2.** Mortality and hospitalization according to Naples groups

| | NPS Group 0 (n=22) | NPS Group 1 (n=62) | NPS Group 2 (n=17) | p |
|---|---|---|---|---|
| Mortality | 3 (13.6%) | 8 (12.9%) | 7 (41.2%) | **0.023** |
| Hospitalization | 10 (45.5%) | 25 (40.3%) | 13 (76.5%) | 0.071 |
| BNP | 990 (45–15757) | 268.5 (10–14256) | 1647 (73–3597) | 0.231 |
| Troponin | 11 (3–70) | 10.5 (3–628) | 12 (3–221) | 0.554 |
| CRP | 0.0073 (0.00–0.01) | 0.0031 (0.00–0.31) | 0.0078 (0.00–0.05) | 0.170 |

BNP: B-type natriuretic peptide; CRP: C-reactive protein; NPS: Naples prognostic score.

**Table 3.** Multivariable models for detecting mortality in PAH patients

| | Model 1 | | Model 2 | |
|---|---|---|---|---|
| | OR, 95% CI | p | OR, 95% CI | p |
| Troponin | 0.992 (0.967–1.017) | 0.519 | 0.992 (0.968–1.017) | 0.548 |
| Sex, F | 2.563 (0.211–31.057) | 0.460 | 4.240 (0.252–71.356) | 0.316 |
| CRP | 1.077 (0.995–1.166) | 0.265 | 1.107 (0.998–1.157) | 0.255 |
| Total protein | 1.106 (0.932–1.312) | 0.250 | 1.151 (0.970–1.366) | 0.108 |
| Urea | 1.042 (0.980–1.108) | 0.190 | 1.037 (0.965–1.113) | 0.322 |
| Uric acid | 1.532 (0.961–2.442) | 0.073 | 1.697 (0.980–2.937) | 0.059 |
| Age | 1.059 (1.000–1.122) | **0.049** | 1.056 (0.995–1.119) | 0.070 |
| BNP | 1.000 (1.000–1.001) | **0.029** | 1.000 (1.000–1.001) | **0.019** |
| Naples score | - | - | 2.291 (1.033–5.081) | **0.041** |

CRP: C-reactive protein; BNP: B-type natriuretic peptide.

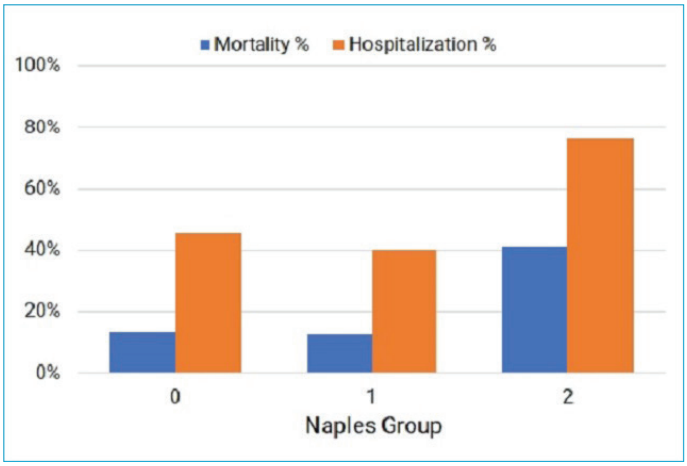


**Figure 1.** Comparison of outcomes in PAH patients across Naples groups. Data presented in the clustered bar graph showed a higher hospitalization and mortality rate in Group 2.

**Table 4.** Performances of models

| | –2 log-likelihood | Nagelkerke's R2 | Brier-scaled |
|---|---|---|---|
| Model 1 | 28.055 | 0.502 | 0.315 |
| Model 2 | 26.971 | 0.527 | 0.331 |

## Discussion

Several risk assessment parameters have hitherto been described for PAH patients. Among them, 6MWD, WHO-functional class (WHO-FC), and BNP/NT-proBNP levels are well defined.[1] In our study, the BNP values of all patients were evaluated. Not surprisingly, BNP levels were found to be an independent predictor of mortality in our study.

NPS has been studied first and predominantly in gastrointestinal tract malignancies.[9,14-17] Inflammatory and nutritional indexes have been studied in the literature to establish the prognosis of various diseases, including cirrhosis and Cushing's disease.[18,19] Lately, several studies have been published on STEMI and NPS. Birdal et al.[10] showed that NPS was reversely associated with discharge LVEF in STEMI patients. Saylik et al.[13] demonstrated that NPS was independently associated with long-term mortality in patients with STEMI undergoing primary percutaneous coronary intervention. Similarly, Erdogan et al.[20] found an association between NPS and in-hospital and follow-up outcomes in STEMI patients.

Two recent studies have investigated the relationship between NPS and the prognosis of HF patients. Kilic et al.[12]

demonstrated a strong correlation between NPS and mortality in HF. Erdogan et al.[11] showed that NPS was associated with mortality and rehospitalization in patients with decompensated HF.

The above-mentioned studies contributed to the cardiology literature on patients with STEMI and HF. Apart from these, there are some noteworthy studies. Karakoyun et al.[21] found that NPS may be useful in predicting the risk of acute kidney injury in STEMI patients undergoing primary PCI. Ozkan et al.[22] studied systemic immune-inflammation index (SII) and NPS for predicting coronary artery severity in patients undergoing coronary computed tomographic angiography. Unlike the other studies discussed, they reported that SII may have a net predictive effect while NPS may not.

It is generally accepted that inflammation plays a key role in the pathogenesis of PAH.[23,24] As far as we know, no studies have been conducted that address the relationship between NPS and the prognosis of patients with PH. Because NPS is a relatively new score and PAH is a rare disease, our study provided the first contribution to the literature in this respect. NPS, a simple and easily calculated risk score, may help identify high-risk PAH patients.

A few limitations of this study: First, the relatively small patient population is due to the disease's low prevalence and single-center design. Confirmation and generalizability of our findings can be tested through multicenter studies with larger patient populations. Second, inability to access 6MWD and WHO-FC data for most patients due to retrospective design. Therefore, head-to-head comparison of NPS with other prognostic markers has not been possible.

## Conclusion

We found an association between NPS and worse outcomes in patients with PAH. NPS, a simple and readily calculated prognostic score, may help predict the clinical course of PAH patients.

### Disclosures

**Ethics Committee Approval:** The study was approved by the Ethics Committee of Ankara City Hospital (No: E1-23-3553, dated 10.05.2023).

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

**Authorship Contributions:** Concept – S.K.; Design – O.T.; Supervision – O.T.; Fundings: O.T.; Materials – E.A.; Data collection and/or processing – E.A.; Analysis and/or interpretation – S.K.; Literature review – E.A.; Writing – S.K.; Critical review – O.T.

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