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# Modified naples prognostic score as a potential predictor for coronary slow flow: a retrospective observational study

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**Abstract**

The Naples prognostic score (NPS) predicts patient survival in gastroesophageal cancer using parameters related to nutritional and inflammatory status. These parameters include risk factors for coronary endothelial dysfunction except for low total cholesterol. Therefore, we modified the score (mNPS) to include high cholesterol, a risk factor for coronary endothelial dysfunction. We aimed to evaluate the relationship between mNPS and the angiographic epicardial coronary slow flow phenomenon (CSFP). This retrospective study included 301 patients with coronary slow flow who underwent coronary angiography between 2018 and 2022. The mNPS parameters were calculated and the population was divided into three groups based on the calculated parameters. Angiographic findings were classified in the left anterior descending (LAD), circumflex (Cx), right coronary (RCA) arteries, and three coronary arteries together. Statistical analyses were performed to identify mNPS as predictors of a slow flow phenomenon. Participants were divided into mNPS Group 1 (n=63), mNPS Group 2 (n=201), and mNPS Group 3 (n=37). No significant differences were observed in age, gender, or medications among the mNPS groups. The RCA had a statistically significant association with mNPS groups for slow flow phenomenon (p=0.006). Considering all three coronary arteries, the association with mNPS groups was also significant (p=0.005). White blood cell and lymphocyte counts showed significant differences. Compared with group 1, group 3 had 4.11 times more coronary artery slow flow. Our study suggests that the mNPS, integrating nutritional and inflammatory parameters along with high cholesterol, holds promise as a potential predictor for the coronary slow flow phenomenon. This could impact risk stratification and clinical management in this patient group.

**Keywords:** Modified naples, prognostic score, coronary slow flow

## Introduction

The Naples prognostic score (NPS) is a scoring system used to predict patient survival in certain types of gastroesophageal cancer, such as esophageal cancer. This score is based on parameters that reflect the patient's nutritional and inflammatory status and is based on total cholesterol, albumin, lymphocyte-to-monocyte ratio (LMR), and neutrophil-lymphocyte ratio (NLR) [1,2]. Many studies have shown that low albumin, high cholesterol, and chronic inflammation are related to an increased risk of coronary slow flow phenomenon (CSFP) as early stage of coronary artery disease [3-5]. The combination of these risk factors corresponds to the NPS parameters except the cholesterol level. The high serum cholesterol level is a risk factor for coronary endothelial dysfunction and coronary artery disease [6]. As so, the NAPLES score was modified by changing the cholesterol value from low to high. Modified NAPLES (mNPS) might be associated with coronary slow flow by replacing a low cholesterol value with a high value. In this study, we aimed to evaluate the relationship between the modified NPS and angiographic epicardial CSFP.

## Material and Methods

### Study design and participants

This study was designed as a retrospective observational study and included patients with coronary slow-flow who underwent coronary angiography for suspected coronary artery disease.

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The participants were recruited from in a single center between 2018 and 2022. The local ethics committee approved the study's protocol. Clinical and laboratory data were collected from the medical records of the eligible participants. The following parameters of mNPS were recorded for each patient.

***Albumin level (normal: ≥4g/dl):*** The serum albumin level, which is an indicator of nutritional status and anti-inflamatory, was measured using standard laboratory methods. serum albumin

***Lymphocyte-to-monocyte ratio (LMR, normal: >4.44):*** The LMR, calculated as the absolute lymphocyte count divided by the absolute monocyte count, was determined from the complete blood count (CBC) results.

***Neutrophil-to-lymphocyte ratio (NLR, normal: ≤2.96):*** The NLR, obtained from the CBC, was calculated as the absolute neutrophil count divided by the absolute lymphocyte count. This parameter reflects the inflammatory status of the patient.

***Cholesterol level (total cholesterol normal: <180 mg/dl):*** The serum cholesterol level was measured using standard laboratory techniques.

***Angiographic findings:*** Coronary angiograms of the participants were reviewed by experienced cardiologists who were blinded to the patients' mNPS scores. Angiographic coronary slow flow phenomenon were identified and classified according to standard criteria [7]. The TIMI (Thrombolysis in Myocardial Infarction) frame count method was used to measure coronary flow in the left anterior descending (LAD), circumflex (Cx), and right coronary (RCA) arteries. The study investigated the relationship between mNPS groups and the occurrence of coronary slow flow phenomenon in three major coronary arteries: LAD, CX, RCA and three coronary arteries togather.

### Calculation of the modified naples prognostic score (mNPS)

mNPS was calculated for each patient using the following chart (Figure 1).

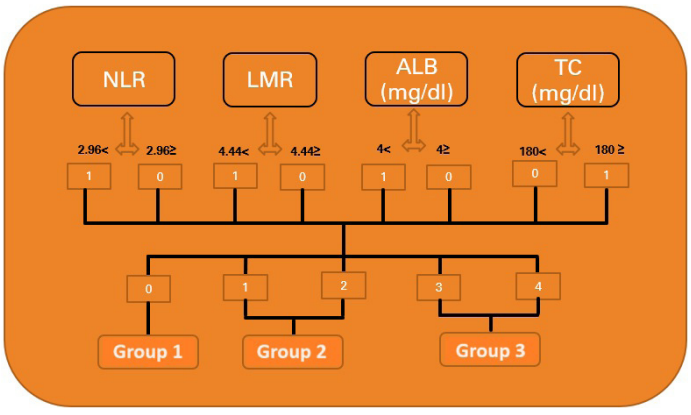


**Figure 1.** Defnition and criteria of mNPS groups, mNPS: modified Naples prognostic score, NLR: neutrophil-lymphocyte ratio, LMR: lymphocyte-monocyte ratio, ALB: albumin, TC: total cholesterol

Based on the calculated parameters (albumin level, LMR, NLR, and total cholesterol level), patients were categorized. The patients were subsequently divided into three groups: those with scores of 0 were placed in group 1 (all four parameters had normal values); those with scores of 1 or 2 were placed in group 2 (one or two altered values); and those with scores of 3 or 4 were placed in group 3 (three or four altered values).

### Statistical analysis

Statistical analyses were performed using SPSS. To describe the demographic and clinical features of the study population, descriptive statistics were used. Based on their distribution, continuous variables have been defined as mean standard deviation (SD) or median with interquartile range (IQR). Categorical variables were expressed as frequencies and percentages. To assess the relationship between the mNPS and the slow flow phenomenon, the study population was divided into two groups based on the presence or absence of these angiographic findings. The mNPS values were compared between the groups using appropriate statistical tests (e.g., independent t-test or Mann-Whitney U test). A multivariable logistic regression analysis was conducted to identify independent predictors of slow flow phenomenon. Variables found to be significantly associated with the outcomes in univariate analysis were included in the regression models. For all analyses, a two-tailed p-value of 0.05 was accepted as statistically significant.

## Results

The demographic characteristics of the study population, including age and gender distribution, are presented in Table 1. The study included 301 participants who had coronary angiography for suspected coronary artery disease. Based on the calculated mNPS, the study population was divided into three groups: mNPS group 1 (n=63), mNPS group 2 (n=201), and mNPS group 3 (n=37). The mean ages of the participants were 57±9, 61±10, and 64±11 years, respectively, and 44 (69.8%), 155 (77.1%), and 29 (78.4%) were male, respectively. There were no statistically significant differences in age, gender distribution, hypertension, smoking, use of ACE-I, ARB, beta-blocker, NDP KKB, DP KKB, statin, or ASA medications among the three mNPS groups (Table 1).

**Table 1.** The demographic and baseline characteristics

| Characteristics | G1 (n=63) | G2 (n=201) | G3 (n=37) | P value |
|---|---|---|---|---|
| **Age (years), mean±SD** | 57±9 | 61±10 | 64±11 | 0.219 |
| **Gender (male), n (%)** | 44 (69.8) | 155 (77.1) | 29 (78.4) | 0.463 |
| **Hypertension, n (%)** | 36 (57.1) | 111 (55.2) | 26 (70.3) | 0.235 |
| **Diabetes mellitus, n (%)** | 14 (22.2) | 57 (28.4) | 16 (43.2) | 0.078 |
| **Smoking, n (%)** | 8 (12.7) | 17 (8.5) | 3 (8.1) | 0.579 |
| **Ace-I, n (%)** | 15 (23.8) | 43 (21.4) | 10 (27.0) | 0.728 |
| **ARB, n (%)** | 5 (7.9) | 15 (7.5) | 6 (16.2) | 0.214 |
| **BBloker, n (%)** | 18 (28.6) | 72 (35.8) | 15 (40.5) | 0.427 |
| **NDP CCB, n (%)** | 0 (0) | 6 (3.0) | 2 (5.4) | 0.237 |
| **DP CCB, n (%)** | 3 (4.8) | 18 (9.0) | 6 (16.2) | 0.154 |
| **Statin, n (%)** | 17 (27.0) | 48 (23.9) | 11 (29.7) | 0.707 |
| **ASA, n (%)** | 24 (38.1) | 89 (44.3) | 14 (37.8) | 0.583 |

ACEinh: Angiotensin-converting-enzyme inhibitors, ARBs: Angiotensin receptor blockers, NDP KKB: non-dihydropyridine calcium channel blockers, DP CCB:dihydropyridine calcium channel blockers, ASA: acetylsalicylic acid

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There were no statistically significant differences in glucose, red blood cell count, creatinine, platelet count, and C-reactive protein (CRP) levels among groups (Table 2). However, significant differences were observed in white blood cell count and lymphocyte count among the three mNPS groups. The white blood cell count was higher in mNPS Group 2 compared to mNPS Group 1 and significantly lower in mNPS Group 3 compared to both mNPS Group 1 and mNPS Group 2. Similarly, the lymphocyte count was significantly lower in mNPS Group 3 compared to both mNPS Group 1 and mNPS Group 2 (Table 2).

The distribution of the coronary slow flow phenomenon in each mNPS group was analyzed (Table 3). In the LAD, CX, and RCA, the percentage of patients with slow flow phenomenon showed an increasing trend from mNPS Group 1 to mNPS Group 3. The association between mNPS groups and slow flow phenomenon in the RCA was found to be statistically significant (p=0.006). However, statistical significance was not reached for isolated LAD and CX alona. Notably, when considering the slow flow phenomenon in all three major coronary arteries (total epicardial coronary bed), the association with mNPS groups was also statistically significant (p=0.005) (Table 3).

We designed the multivariable logistic regression analysis using three different models due to the small sample size (Table 4).

Model 1 was conducted and group 3 had 4.11 times more coronary artery slow flow than reference group 1. Similarly, in model 2 and model 3, significantly more coronary slow flow was shown in group 3.

**Table 2.** Laboratory parameters

| | G1 | G2 | G3 | P value |
|---|---|---|---|---|
| **Glucose, mg/dL** | 101 (92-136) | 104 (93-128) | 110 (94-134) | 0.100 |
| **Red blood cell count, cells/µL** | 5.1±1.96 | 4.97±1.11 | 4.83±1.28 | 0.634 |
| **Creatinine, mg/dL** | 0.9±0.16 | 1.05±0.73 | 1.15±0.37 | 0.119 |
| **White blood cell count, cells/µL** | 7.66±1.85 | 7.95±2.18 | 3.79±3.45 | <0.001 |
| **Platelet count, cells/µL** | 221 (197-264) | 235 (197-280) | 247 (218-338) | 0.646 |
| **CRP, mg/dL** | 2.5 (2.0-4.1) | 3.0 (2.0–7.0) | 5.7 (2.0-20.0) | 0.063 |
| **Lymphocyte count, cells/µL** | 2.62±0.71 | 2.29±0.85 | 1.85±0.65 | <0.001 |

CRP: C-reactive protein

**Table 3.** The distribution slow-flow of coronary arteries and mNPS

| Slow-flow | G1 (n=63) | G2 (n=201) | G3 (37) | P value |
|---|---|---|---|---|
| **LAD slow-flow** | 7 (11.1) | 34 (16.9) | 11 (29.7) | 0.058 |
| **CX slow-flow** | 3 (4.8) | 15 (7.5) | 4 (10.8) | 0.527 |
| **RCA slow-flow** | 7 (11.1) | 40 (19.9) | 14 (37.8) | 0.006 |
| **Three coronary artery slow-flow** | 14 (22.2) | 65 (32.3) | 20 (54.1) | 0.005 |

LAD: left anterior descending artery CX: circumflex artery RCA: right coronary artery , mNPS: modified NAPLES score

**Table 4.** Logistic regression analysis for coronary slow flow

| | G1 (n=63) | G2 (n=201) | G3 (n=37) |
|---|---|---|---|
| **Coronary slow flow** | | | |
| **Number of events, %** | 14 (22.2) | 65 (32.3) | 20 (54.1) |
| **Event, OR (95% CI)** | | | |
| **Model 1: unadjusted** | 1 [Reference] | 1.67 (0.86-3.24) | 4.11 (1.71-9.90) |
| **Model 2: adjusted for age** | 1 [Reference] | 1.65 (0.85-3.22) | 4.07 (1.69-9.82) |
| **Model 3: adjusted for all covariates[a]** | 1 [Reference] | 1.62 (0.83-3.20) | 4.02 (1.62-9.93) |

Abbreviations: OR, Odds ratio; ACEinh: Angiotensin-converting-enzyme inhibitors, ARB: Angiotensin receptor blocker

aIncludes demographics (age and sex); comorbidities (hypertension, diabetes mellitus, smoking, coronary artery disease); medications; asetil salisylic acid, clopidogrel, ticagrelor, calcium canal bloker, ACEinh, ARB

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## Discussion

The epicardial coronary slow flow phenomenon is frequently observed during angiography in daily clinical practice. CSFP is considered a consequence of endothelial dysfunction and promotes the onset and progression of atherosclerosis by altering endothelial permeability, activating the immune response, and promoting atherothrombosis [8].

CSFP is a condition characterized by delayed contrast opacification and decreased coronary blood flow velocity in the absence of significant epicardial coronary artery stenosis [7]. Although the precise pathophysiological mechanisms underlying CSFP remain incompletely understood, several risk factors have been proposed in the literature [9]. Some of these include chronic inflammation, atherosclerosis, hyperlipidemia, hypertension, thrombophilic states, smoking, microvascular dysfunction, and psychological stress [9]. Chronic low-grade inflammation has been recognized as a key contributor to endothelial dysfunction and impaired vasomotor regulation in the coronary arteries. Inflammatory mediators lead to reduced vasodilation and increased vasoconstriction. Consequently, the altered vascular tone contributes to the manifestation of CSFP [10]. Hyperlipidemia has also been implicated as a potential risk factor for CSFP. Excess cholesterol can accumulate in the arterial wall and trigger an inflammatory response [11]. The formation of lipid-laden foam cells and the subsequent release of pro-inflammatory cytokines promote endothelial dysfunction and impede the production of nitric oxide, leading to impaired endothelium-dependent vasodilation. Additionally, high cholesterol levels can induce oxidative stress, further exacerbating endothelial dysfunction and contributing to the pathogenesis of CSFP [12,13]. Albumin, as a negative acute-phase reactant, can be influenced by inflammatory mediators. In conditions of heightened inflammation, the liver's synthesis of albumin may decrease. Also, albumin possesses anti-inflammatory properties and serves as a free radical scavenger, combating oxidative stress. So, hypoalbuminemia can contribute to endothelial dysfunction and cause CSFP [14]. The investigation of CSFP may benefit from considering the combined influence of inflammatory status, nutritional status, and hypercholesterolemia, as these factors could play an important role in its pathogenesis. The study investigated the occurrence of CSFP in different coronary arteries based on the mNPS groups. While there was an increasing trend in the percentage of patients with slow flow phenomenon from mNPS Group 1 to mNPS Group 3 in the LAD and CX coronary arteries, these trends did not reach statistical significance, suggesting a lack of association between mNPS and slow flow in these arteries alone. However, in the RCA, the occurrence of slow flow phenomenon was significantly higher in mNPS Group 3 compared to mNPS Group 1 and mNPS Group 2, indicating a potential relationship between mNPS and slow flow in the RCA. However, when considering slow flow phenomenon in all three major coronary arteries (total epicardial coronary bed), the association with mNPS groups was found to be statistically significant. This observation suggests that the combined effect of mNPS parameters might play a more significant role in predicting the total coronary slow flow phenomenon than isolated involvement of specific coronary arteries. The fact that mNPS is associated with slow flow of all three coronary arteries rather than the isolated coronary arteries indicate systemic involvement of the total coronary artery bed.

Ultimately, it is important to evaluate a phenomenon with multiple risk factors using a scoring system that incorporates a combination of nutritional status, chronic inflammation, and cholesterol parameters. The pathophysiological mechanism underlying the association between mNPS and CSFP may be attributed to the interplay between inflammation, nutritional status, and endothelial dysfunction. Inflammatory mediators are known to induce endothelial dysfunction, leading to impaired vasodilation and increased microvascular resistance in the coronary arteries [15]. Additionally, a low lymphocyte count may indicate compromised immune function, which could further exacerbate inflammation and endothelial dysfunction, contributing to the development of CSFP [16]. Moreover, altered nutritional status, as reflected by the mNPS, may influence endothelial function and contribute to the coronary slow flow phenomenon through various mechanisms, including oxidative stress and impaired nitric oxide bioavailability [14].

## Limitations

It's important to acknowledge the limitations of this study. Firstly, the retrospective nature of the study design may introduce selection bias and limit causal inferences. Secondly, the study's single-center design might limit the generalizability of the findings to other populations. Also, the cross-sectional nature of the data prevents establishing temporal relationships between mNPS and angiographic findings. Lastly, unmeasured confounding variables could influence the observed associations.

## Conclusion

In this study, we aimed to evaluate the relationship between the mNPS and CSFP in patients with undervented diagnostic coronary angiography. The mNPS, which incorporates parameters reflecting nutritional and inflammatory status as well as high serum cholesterol, may serve as a potential predictor for these CSFP. Understanding the association between mNPS and CSFP could have implications for risk stratification and clinical management in this patient population. Further research with larger prospective studies is warranted to validate our findings and explore the clinical utility of mNPS in predicting epicardial coronary slow flow phenomenon.

**Conflict of Interests**

*The authors declare that there is no conflict of interest in the study.*

**Financial Disclosure**

*The authors declare that they have received no financial support for the study.*

**Ethical Approval**

*Design of the study was approved by the regional ethical research committee in Sultan Abdulhamid Han Trainin and Research Hospital (Date 24.02.2023, reference number: 2023/4).*

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