

# Prognostic Impact of the Naples Prognostic Score in Patients With Type 2 Cardiorenal Syndrome: A Retrospective Cohort Study

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## Research Article

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# Abstract

## Objective:

Type 2 cardiorenal syndrome (CRS-2) is characterized by progressive renal dysfunction secondary to chronic heart failure and is associated with high mortality. The Naples Prognostic Score (NPS), integrating inflammatory and nutritional parameters, has emerged as a prognostic marker in cardiovascular diseases. This study aimed to investigate the prognostic value of the Naples Prognostic Score for predicting in-hospital mortality in patients with CRS-2.

## Methods:

This retrospective cohort study included 101 adult patients hospitalized with CRS-2 in the cardiology department of a tertiary referral center between June 2021 and August 2024. NPS was calculated using admission laboratory parameters, and patients were stratified into low NPS (Stage 1–2) and high NPS (Stage 3) groups. Clinical variables including age, comorbidities, and New York Heart Association (NYHA) functional class were recorded. Univariable and multivariable logistic regression analyses were performed to identify predictors of in-hospital mortality. Discriminative performance of NPS was evaluated using receiver operating characteristic (ROC) analysis.

## Results:

In-hospital mortality was significantly higher in the high NPS group compared with the low NPS group (54.5% vs. 11.8%,  $p < 0.001$ ). In multivariable analysis, high NPS remained independently associated with in-hospital mortality (OR: 4.79, 95% CI: 1.34–17.15,  $p = 0.016$ ), together with older age (OR: 1.09, 95% CI: 1.02–1.17,  $p = 0.007$ ) and higher NYHA class (OR: 5.21, 95% CI: 1.97–13.81,  $p = 0.001$ ). ROC analysis showed good predictive ability of NPS (AUC: 0.816; optimal cut-off  $\geq 2$ ; sensitivity 92.3%, specificity 62.7%).

## Conclusion:

The Naples Prognostic Score may provide a simple and practical tool for early risk stratification of patients with type 2 cardiorenal syndrome at hospital admission.

## HIGHLIGHTS

- The Naples Prognostic Score was independently associated with in-hospital mortality in patients with type 2 cardiorenal syndrome.
- High NPS (Stage 3) was linked to significantly higher mortality compared with lower scores.
- NPS demonstrated good discriminative ability for predicting in-hospital mortality (AUC 0.816).

- As a score derived from routine laboratory parameters, NPS may represent a simple tool for early risk stratification in CRS-2 patients.

## INTRODUCTION

Cardiorenal syndrome (CRS) is a complex clinical condition characterized by the bidirectional pathophysiological interaction between cardiac and renal dysfunction. According to the Acute Dialysis Quality Initiative (ADQI) classification, Type 2 cardiorenal syndrome (CRS-2) refers to chronic abnormalities in cardiac function leading to progressive deterioration of renal function (1).

CRS-2 is associated with substantial morbidity and mortality. Its pathogenesis involves a multifactorial interplay of venous congestion, neurohormonal activation, systemic inflammation, oxidative stress, and malnutrition (2–4). Emerging evidence suggests that the combined evaluation of inflammatory burden and nutritional status may provide more comprehensive prognostic information in heart failure and cardiorenal populations.

The Naples Prognostic Score (NPS) is a composite index integrating serum albumin and total cholesterol as markers of nutritional status, together with neutrophil-to-lymphocyte ratio (NLR) and lymphocyte-to-monocyte ratio (LMR) as markers of systemic inflammation. Initially developed in oncological populations (5), NPS has subsequently demonstrated prognostic value in cardiovascular cohorts (6, 7). However, data regarding its utility in patients with CRS-2 remain limited.

To our knowledge, the prognostic significance of the Naples Prognostic Score in patients with type 2 cardiorenal syndrome has not been previously investigated. Therefore, this study aimed to evaluate the association between NPS and in-hospital mortality in patients with CRS-2.

## METHODS

This retrospective observational cohort study was conducted in the cardiology department of a tertiary referral hospital between June 1, 2021 and August 1, 2024. Ethical approval was obtained from the local ethics committee (Approval date: September 19, 2024; No: 05). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patients were eligible for inclusion if they met the following criteria:

- Age  $\geq 18$  years
- Diagnosis of Type 2 cardiorenal syndrome (CRS-2)
- Hospitalization in the cardiology department

The diagnosis of CRS-2 was established in patients with chronic heart failure accompanied by progressive deterioration of renal function, in accordance with the Acute Dialysis Quality Initiative classification (1,2).

The following variables were retrieved from electronic medical records:

- Age and sex
- Diabetes mellitus (DM)
- Hypertension (HT)
- Atrial fibrillation (AF)
- New York Heart Association (NYHA) functional class
- Admission creatinine
- Discharge creatinine
- Estimated glomerular filtration rate (eGFR)

NYHA functional class was assessed at the time of hospital admission based on clinical evaluation. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. No significant missing data were present for the variables included in the analysis.

The Naples Prognostic Score (NPS) was calculated using laboratory parameters obtained at hospital admission (5). The Naples Prognostic Score was calculated based on four parameters: albumin  $<4$  g/dL, total cholesterol  $\leq 180$  mg/dL, neutrophil-to-lymphocyte ratio  $\geq 2.96$ , and lymphocyte-to-monocyte ratio  $\leq 4.44$ . Each parameter was assigned 1 point, yielding a total score ranging from 0 to 4.

### **NPS Staging**

- Stage 1: 0–1
- Stage 2: 2
- Stage 3: 3–4

### **Study Endpoints**

#### **Primary Endpoint**

- In-hospital mortality

#### **Secondary Endpoints**

- Discharge status
- Requirement for routine hemodialysis among discharged patients

### **Statistical Analysis**

All statistical analyses were performed using IBM SPSS Statistics (Version 26, IBM Corp., Armonk, NY, USA). The distribution of continuous variables was assessed using the Kolmogorov–Smirnov test. Normally distributed variables were expressed as mean  $\pm$  standard deviation (SD), whereas non-normally

distributed variables were presented as median (minimum–maximum). Categorical variables were reported as counts and percentages (%).

Comparisons between two groups were performed using the independent samples t-test for normally distributed continuous variables and the Mann–Whitney U test for non-normally distributed variables. Categorical variables were compared using the chi-square ( $\chi^2$ ) test or Fisher's exact test when expected cell counts were <5.

To identify independent predictors of in-hospital mortality, multivariable logistic regression analysis was conducted. Variables considered clinically relevant and those with a p-value <0.10 in univariable analysis were entered into the multivariable model. Results were reported as odds ratios (ORs) with 95% confidence intervals (CIs). To avoid model overfitting, the number of variables included in the multivariable logistic regression model was limited according to the event-per-variable principle.

The discriminative performance of the Naples Prognostic Score (NPS) for predicting in-hospital mortality was evaluated using receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC) was calculated, and the optimal cut-off value was determined using the Youden index. An AUC of 0.70–0.80 was considered acceptable, 0.80–0.90 good, and >0.90 excellent discrimination.

All tests were two-tailed, and a p-value <0.05 was considered statistically significant.

## RESULTS

A total of 101 patients with CRS-2 were included in the analysis. According to the Naples Prognostic Score (NPS), 68 patients (67.3%) were classified as low-risk (Stage 1–2) and 33 patients (32.7%) as high-risk (Stage 3). Baseline demographic and clinical characteristics of the study population are presented in Table 1.

Table 1  
Baseline Characteristics According to Naples Prognostic Score Groups

| Variable                                                                                                                                                   | Low NPS (Stage 1–2)(n = 68) | High NPS (Stage 3)(n = 33) | p-value |
|------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|----------------------------|---------|
| Age (years)                                                                                                                                                | 68.94 ± 12.82               | 74.70 ± 11.35              | 0.025   |
| Admission creatinine (mg/dL)                                                                                                                               | 2.3 ± 1.0                   | 2.7 ± 1.3                  | 0.134   |
| eGFR (mL/min/1.73m²)                                                                                                                                       | 29.88 ± 12.72               | 25.03 ± 11.62              | 0.048   |
| Ejection fraction (%)                                                                                                                                      | 39.1 ± 12.1                 | 32.8 ± 10.7                | 0.009   |
| Albumin (g/dL)                                                                                                                                             | 3.28 ± 0.56                 | 3.28 ± 0.53                | 0.978   |
| Total cholesterol (mg/dL)                                                                                                                                  | 164.8 ± 63.4                | 134.2 ± 34.9               | 0.002   |
| NLR                                                                                                                                                        | 3.4 ± 2.5                   | 9.9 ± 8.6                  | < 0.001 |
| LMR                                                                                                                                                        | 4.8 ± 2.1                   | 1.6 ± 0.9                  | < 0.001 |
| Sex (Female), n (%)                                                                                                                                        | 28 (41.2)                   | 15 (45.5)                  | 0.36    |
| Diabetes mellitus, n (%)                                                                                                                                   | 27(39.7)                    | 15(45.5)                   | 0.93    |
| Hypertension, n (%)                                                                                                                                        | 47(69.1)                    | 22(66.7)                   | 1.00    |
| Atrial fibrillation, n (%)                                                                                                                                 | 21(30.9)                    | 14(42.4)                   | 0.86    |
| NYHA Class 1, n (%)                                                                                                                                        | 6 (8.8)                     | 1 (3.0)                    | 0.008   |
| NYHA Class 2, n (%)                                                                                                                                        | 23 (33.8)                   | 6 (18.2)                   |         |
| NYHA Class 3, n (%)                                                                                                                                        | 31 (45.6)                   | 15 (45.5)                  |         |
| NYHA Class 4, n (%)                                                                                                                                        | 8 (11.8)                    | 11 (33.3)                  |         |
| Abbreviations: NPS – Naples Prognostic Score; NYHA – New York Heart Association; NLR – neutrophil-to-lymphocyte ratio; LMR – lymphocyte-to-monocyte ratio. |                             |                            |         |

The mean age was significantly higher in the high NPS group compared with the low NPS group (74.70 ± 11.35 vs. 68.94 ± 12.82 years; p = 0.025). Admission creatinine levels were numerically higher in the high NPS group (2.68 ± 1.28 vs. 2.29 ± 0.96 mg/dL), although this difference did not reach statistical significance (p = 0.134).

Left ventricular ejection fraction (LVEF) was significantly lower in patients with high NPS (32.82 ± 10.69 vs. 39.13 ± 12.08%; p = 0.009), suggesting more advanced cardiac dysfunction among high-risk patients.

Significant differences were observed in several components related to inflammatory and nutritional status. Patients in the high NPS group exhibited markedly elevated neutrophil-to-lymphocyte ratio and significantly lower lymphocyte-to-monocyte ratio (both p < 0.001). Serum albumin levels did not differ

significantly between the groups ( $p = 0.978$ ), whereas total cholesterol levels were significantly lower in the high NPS group ( $134.15 \pm 34.91$  vs.  $164.56 \pm 62.97$  mg/dL;  $p = 0.002$ ).

Regarding categorical variables, no significant differences were observed in female sex distribution, diabetes mellitus, hypertension, or atrial fibrillation between the two groups (all  $p > 0.05$ ).

Clinical outcomes are summarized in Table 2. In-hospital mortality was significantly higher in the high NPS group compared with the low NPS group (54.5% vs. 11.8%;  $p < 0.001$ ). Conversely, discharge rates were significantly higher among patients with low NPS (88.2% vs. 45.5%;  $p < 0.001$ ). The requirement for routine hemodialysis was also more frequent in the high NPS group (24.2% vs. 5.9%;  $p = 0.017$ ).

Table 2  
Clinical Outcomes According to Naples Prognostic Score Groups

| Outcome              | Low NPS (Stage 1–2) | High NPS (Stage 3) | p-value |
|----------------------|---------------------|--------------------|---------|
| Mortality            | 8(11.8%)            | 18(54.5%)          | < 0.001 |
| Discharge            | 60(88.2%)           | 15(45.5%)          | < 0.001 |
| Routine hemodialysis | 4(5.9%)             | 8(24.2%)           | 0.017   |

The results of the univariable and multivariable logistic regression analyses for predictors of in-hospital mortality are presented in Table 3. In univariable analysis, high NPS (Stage 3) was strongly associated with in-hospital mortality (OR: 9.00, 95% CI: 3.29–24.63;  $p < 0.001$ ). Age was also significantly associated with mortality (OR: 1.10 per year increase, 95% CI: 1.04–1.17;  $p = 0.001$ ). Likewise, a higher NYHA functional class was significantly related to increased mortality risk (OR: 6.28, 95% CI: 2.73–14.46;  $p < 0.001$ ).

Table 3

**Univariable and multivariable logistic regression analyses for in-hospital mortality in CRS-2 patients**  
 Outcome: In-hospital mortality (EX = 1). Multivariable model includes High NPS, Age, NYHA class, and Ejection Fraction (n = 101).

| Variable (unit / comparison)                                                                                                                                                                                    | Univariable OR (95% CI) | p value | Multivariable OR (95% CI) | p value |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|---------|---------------------------|---------|
| High NPS (Stage 3) vs Low (Stage 1–2)                                                                                                                                                                           | 9.00 (3.29–24.63)       | < 0.001 | 4.79 (1.34–17.15)         | 0.016   |
| Age (years)                                                                                                                                                                                                     | 1.10 (1.04–1.17)        | < 0.001 | 1.09 (1.02–1.17)          | 0.007   |
| Ejection Fraction (%)                                                                                                                                                                                           | 0.99 (0.95–1.03)        | 0.544   | 0.99 (0.94–1.04)          | 0.639   |
| Admission creatinine (mg/dL)                                                                                                                                                                                    | 0.88 (0.57–1.36)        | 0.558   | —                         | —       |
| Diabetes mellitus (yes)                                                                                                                                                                                         | 0.92 (0.37–2.25)        | 0.849   | —                         | —       |
| Hypertension (yes)                                                                                                                                                                                              | 1.05 (0.31–3.59)        | 0.941   | —                         | —       |
| Atrial fibrillation (yes)                                                                                                                                                                                       | 1.66 (0.66–4.16)        | 0.281   | —                         | —       |
| NYHA class (per 1 class increase)                                                                                                                                                                               | 6.28 (2.73–14.46)       | < 0.001 | 5.21 (1.97–13.81)         | < 0.001 |
| Abbreviations: CRS-2, type 2 cardiorenal syndrome; NPS, Naples Prognostic Score; OR, odds ratio; CI, confidence interval; EF, ejection fraction; NYHA, New York Heart Association.                              |                         |         |                           |         |
| ORs are expressed per 1-unit increase for continuous variables (Age per year, EF per %, creatinine per mg/dL, NYHA per 1 class). Binary variables are yes vs no; High NPS refers to Stage 3 vs Low (Stage 1–2). |                         |         |                           |         |

In contrast, ejection fraction, admission creatinine level, diabetes mellitus, hypertension, and atrial fibrillation were not significantly associated with in-hospital mortality in the univariable analysis (all  $p > 0.05$ ).

Variables considered clinically relevant (high NPS, age, NYHA class, and ejection fraction) were subsequently entered into the multivariable logistic regression model. In the multivariable analysis, high NPS remained an independent predictor of in-hospital mortality (OR: 4.79, 95% CI: 1.34–17.15;  $p = 0.016$ ). Additionally, older age (OR: 1.09, 95% CI: 1.02–1.17;  $p = 0.007$ ) and higher NYHA functional class (OR: 5.21, 95% CI: 1.97–13.81;  $p = 0.001$ ) were independently associated with mortality. However, ejection fraction was not independently associated with mortality after adjustment for the other variables (OR: 0.99, 95% CI: 0.94–1.04;  $p = 0.639$ ).

The discriminative performance of NPS for predicting in-hospital mortality was evaluated using receiver operating characteristic (ROC) analysis (Table 4). The analysis demonstrated an area under the curve (AUC) of 0.816 (95% CI: 0.710–0.923), indicating good discriminative ability. The optimal cut-off value determined by the Youden index was  $NPS \geq 2$ , yielding a sensitivity of 92.3% and specificity of 62.7%. Although the ROC-derived optimal cut-off value was  $NPS \geq 2$ , group comparisons and regression

analyses were performed using the established NPS staging system (Stage 1–2 vs Stage 3) as described in the original score definition. The receiver operating characteristic curve demonstrating the discriminative performance of the Naples Prognostic Score for predicting in-hospital mortality is shown in Fig. 1.

Table 4  
ROC Analysis of Naples Prognostic Score for Prediction of In-Hospital Mortality

| Variable                                                                                                                                     | AUC   | 95% Confidence Interval | Optimal Cut-off | Sensitivity (%) | Specificity (%) |
|----------------------------------------------------------------------------------------------------------------------------------------------|-------|-------------------------|-----------------|-----------------|-----------------|
| Naples Prognostic Score                                                                                                                      | 0.816 | 0.710–0.923             | ≥ 2             | 92.3            | 62.7            |
| Abbreviations: AUC, area under the curve; CI, confidence interval; NPS, Naples Prognostic Score.                                             |       |                         |                 |                 |                 |
| Optimal cut-off determined by Youden index. Sensitivity and specificity correspond to NPS ≥ 2. Statistical significance defined as p < 0.05. |       |                         |                 |                 |                 |

DISCUSSION

In the present study, we evaluated the prognostic significance of the Naples Prognostic Score (NPS) in patients hospitalized with type 2 cardiorenal syndrome (CRS-2). The principal finding of our study is that elevated NPS (Stage 3) was strongly and independently associated with in-hospital mortality. Even after adjustment for clinically relevant variables including age, NYHA functional class, and left ventricular ejection fraction, high NPS remained an independent predictor of mortality, conferring nearly a five-fold increased risk. Furthermore, the ROC-derived AUC of 0.816 indicates good discriminative capacity, supporting the clinical relevance of this composite score in this high-risk population.

To our knowledge, this is the first study investigating the prognostic value of the Naples Prognostic Score in patients with type 2 cardiorenal syndrome. Given the complex pathophysiology of CRS-2, which involves interactions between cardiac dysfunction, renal impairment, systemic inflammation, and metabolic imbalance, identifying reliable prognostic markers remains clinically important.

CRS represents a complex and multidimensional clinical entity in which cardiac and renal dysfunction perpetuate one another through intertwined hemodynamic and non-hemodynamic pathways. Contemporary literature highlights the central role of venous congestion, neurohormonal activation, systemic inflammation, oxidative stress, endothelial dysfunction, and metabolic derangements in CRS pathobiology (2–4). In CRS-2 specifically, chronic heart failure leads to sustained renal hypoperfusion and congestion, while persistent inflammatory activation and reduced metabolic reserve further accelerate renal deterioration (2–4). Therefore, prognostic tools that capture more than isolated hemodynamic parameters may provide superior risk stratification in this complex syndrome.

The Naples Prognostic Score integrates markers of nutritional status (albumin and total cholesterol) with inflammatory indices (NLR and LMR), thereby reflecting both systemic inflammatory burden and

metabolic reserve. This multidimensional approach is particularly relevant in CRS-2, where inflammation–malnutrition–catabolic imbalance constitutes a key pathophysiological axis. Previous cardiovascular studies have demonstrated associations between NPS and adverse outcomes in ischemic heart disease and post-percutaneous coronary intervention populations (6, 7). However, its prognostic utility in patients with cardiorenal syndrome has remained largely unexplored.

Inflammation-based hematologic indices, particularly neutrophil-to-lymphocyte ratio, have consistently been associated with adverse outcomes in heart failure populations. Recent meta-analyses have shown that elevated NLR independently predicts both short- and long-term mortality in patients with acute heart failure (8, 9). Similarly, malnutrition and protein-energy wasting have emerged as strong prognostic determinants in chronic heart failure and chronic kidney disease populations (10). Importantly, the coexistence of renal dysfunction and malnutrition appears to amplify adverse outcomes. Within this context, NPS may provide additive value by simultaneously capturing inflammatory activation and impaired metabolic resilience, potentially explaining the increased mortality risk observed in our cohort.

Notably, high NPS remained independently associated with mortality even after adjustment for conventional cardiorenal risk markers. This observation suggests that NPS may reflect pathophysiological domains not fully captured by traditional parameters such as creatinine levels or ejection fraction. While NYHA class and age remained strong predictors of mortality, NPS provided incremental prognostic information beyond these established markers. These findings support the concept that composite inflammatory–nutritional indices may enhance risk stratification in complex syndromes such as CRS-2.

The ROC analysis further supports the clinical applicability of the Naples Prognostic Score. An AUC of 0.816 indicates good discriminative performance for predicting in-hospital mortality. Using a cut-off value of  $\geq 2$ , the score demonstrated a sensitivity of 92.3% and specificity of 62.7%. These findings suggest that NPS may serve as a useful tool for identifying high-risk patients at hospital admission.

From a practical perspective, the appeal of NPS lies in its simplicity and availability. All components are derived from routine laboratory parameters, allowing rapid bedside calculation without additional cost. In clinical practice, such easily accessible markers may help clinicians identify patients at higher risk of adverse outcomes and guide closer monitoring and individualized management strategies.

Taken together, our findings suggest that the Naples Prognostic Score represents a biologically plausible and clinically meaningful prognostic marker in patients with type 2 cardiorenal syndrome.

## CONCLUSION

In patients with type 2 cardiorenal syndrome, the Naples Prognostic Score was independently associated with in-hospital mortality and demonstrated good discriminative ability for risk prediction. As a composite index integrating inflammatory and nutritional parameters derived from routine laboratory tests, NPS may provide a simple and practical tool for early risk stratification in this high-risk population.

Further prospective multicenter studies are warranted to confirm these findings and to clarify the potential role of NPS in guiding clinical decision-making in cardiorenal syndrome.

## **LIMITATIONS**

Several limitations of this study should be acknowledged. First, the study was conducted using a retrospective design in a single tertiary care center, which may limit the generalizability of the findings and introduces the potential for selection bias.

Second, the overall sample size and the number of in-hospital mortality events were relatively limited, which may have reduced the statistical power of the analyses and increased the possibility of model overfitting in the multivariable logistic regression model. Therefore, the observed effect sizes should be interpreted with caution.

Third, the Naples Prognostic Score was calculated based solely on laboratory parameters obtained at hospital admission. Dynamic changes in inflammatory and nutritional markers during hospitalization were not evaluated and might provide additional prognostic information.

Fourth, although several clinically relevant covariates were included in the multivariable model, residual confounding cannot be completely excluded due to the observational nature of the study.

Finally, the present study evaluated only in-hospital outcomes, and long-term clinical events were not assessed. Future prospective, multicenter studies with larger patient populations and longer follow-up periods are needed to confirm the prognostic value of the Naples Prognostic Score in patients with type 2 cardiorenal syndrome.

## **Declarations**

### **Acknowledgements**

Not applicable.

### **Statements and Declarations**

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the Sakarya University Ethics Committee (Approval date: September 19, 2024; No: 05). Due to the retrospective nature of the study, the requirement for informed consent was waived by the ethics committee.

### **Author Contributions**

Concept and design: Emre Eynel, Eren Eynel

Supervision: Yusuf Can

Materials: Emre Eynel

Data collection and/or processing: Emre Eynel, Yusuf Can

Analysis and/or interpretation: Eren Eynel, Yusuf Can

Literature review: Emre Eynel

Writing – original draft: Eren Eynel, Yusuf Can

Critical review: Yusuf Can

### **Consent for publication**

Not applicable.

### **Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### **Conflict of Interest**

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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### **Clinical Trial Number**

Not applicable

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## Figures

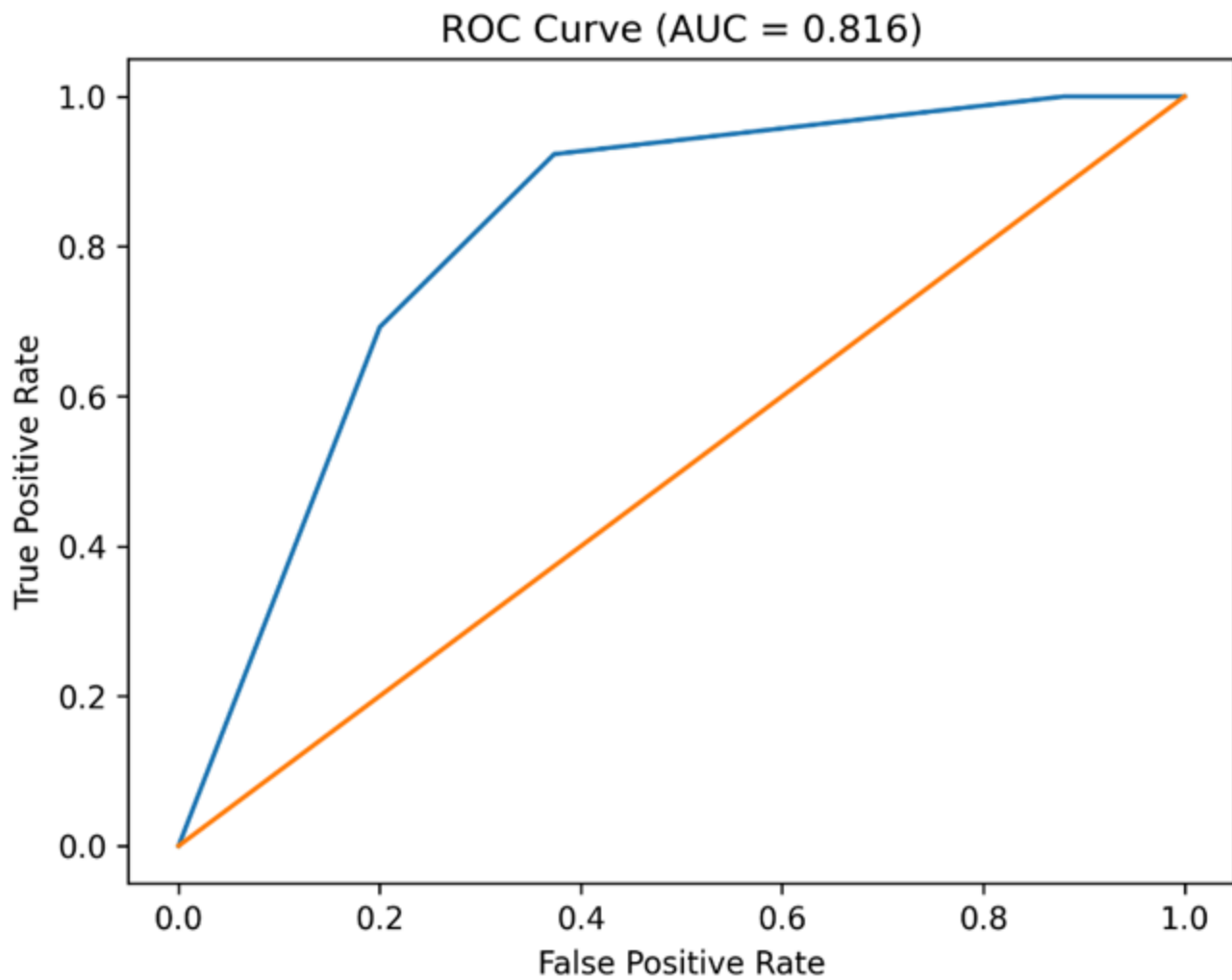


Figure 1

### ROC Curve of the Naples Prognostic Score for Predicting In-Hospital Mortality

The ROC curve demonstrates the discriminative performance of the Naples Prognostic Score for predicting in-hospital mortality (AUC = 0.816).