**Journal of Neonatal Surgery**
***ISSN(Online): 2226-0439***
***Vol. 14, Issue 3 (2025)***
*https://www.jneonatalsurg.com*

OPEN ACCESS

# Evaluating the Role of Pregnancy-Associated Plasma Protein-A (PAPP-A) in Risk Stratification of NSTE-ACS Patients

**Shah Namrata[1], Agarwal Pradeep[2*], Garg Vipul[3], Saini Shakuntala[4], Agarwal Sujata[5]**

[1]PhD. Scholar, Dept. of Biochemistry, SMS Medical College, Jaipur

[2*]Professor, Dept. of Medicine, Mahatma Gandhi Medical College, Jaipur

[3]Associate Professor, Dept of Biochemistry, SMS Medical College, Jaipur

[4]Retd. Senior Professor, Dept. of Biochemistry, SMS Medical College, Jaipur

[5]Professor, Dept. of Medicine, SMS Medical College, Jaipur

***Corresponding Author:**

Dr. Pradeep Agarwal

*Professor, Dept. of Medicine, Mahatma Gandhi Medical College, Jaipur

Cite this paper as: Shah Namrata, Agarwal Pradeep, Garg Vipul, Saini Shakuntala, Agarwal Sujata, (2025) Evaluating the Role of Pregnancy-Associated Plasma Protein-A (PAPP-A) in Risk Stratification of NSTE-ACS Patients. *Journal of Neonatal Surgery*, 14 (3), 298-302.

## ABSTRACT

**Objective:** The primary objective of this study is to evaluate the association between serum Pregnancy-Associated Plasma Protein-A (PAPP-A) levels and the severity of atherosclerosis in patients with Non-ST Segment Elevation Acute Coronary Syndrome (NSTE-ACS), using TIMI risk stratification scores as a clinical assessment tool.

**Methods**: 100 diagnosed patients of NSTE-ACS who underwent coronary angiography were enrolled. The measurements of serum PAPP-A and other laboratory indices were performed within 24 hours after admission. Plasma PAPP-A levels were measured in all patients using the sandwich ELISA method. Patients were stratified based on TIMI risk score (0-7 scale) into low (0–2), intermediate (3–4), and high (5–7) risk groups to assess the association between PAPP-A levels and atherosclerotic severity.

**Results:** Mean serum PAPP-A levels of low-risk patients were (7.47±8.46) followed by high-risk group (7.29±9.23) and medium risk group (6.02±9.13). When statistically analyzed, all risk categories were found similar with respect to serum PAPP-A levels. (P=0.738) The ROC curve analysis for PAPP-A showed an Area Under the Curve (AUC) of 0.521, with a 95% confidence interval of 0.419 to 0.622 (P = 0.7919), indicating poor discriminatory ability. The optimal cut-off value was >2.0 µg/ml, corresponding to the highest Youden index. At this threshold, PAPP-A had a sensitivity of 66.67% (95% CI: 38.4 - 88.2%) and a specificity of 49.41% (95% CI: 38.4 - 60.5%). The positive likelihood ratio (+LR) was 1.32 (95% CI: 0.9 - 2.0) and the negative likelihood ratio (-LR) was 0.67 (95% CI: 0.3 - 1.4).

**Conclusion:** PAPP-A alone does not offer meaningful risk stratification in NSTE-ACS. Further research is warranted to evaluate its value in combination with other markers or scoring systems.

***Keywords:*** *Pregnancy-Associated Plasma Protein-A, non-ST segment elevation acute coronary syndrome, TIMI score*

## 1. INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of death in India, responsible for about 25% of all fatalities.[1] Acute Coronary Syndrome (ACS), which includes STEMI, NSTEMI, and UA(unstable angina), is a major contributor.[2] NSTEMI and UA together constitute non-ST-elevation ACS (NSTE-ACS), marked by the absence of ST-segment elevation on ECG. NSTE-ACS accounts for nearly 70% of ACS cases and poses diagnostic and therapeutic challenges. [3] Its high prevalence and clinical burden make it a significant public health concern. [4]

Pregnancy-associated plasma protein-A (PAPP-A) is an emerging biomarker associated with inflammation and plaque instability. [5-7] It is a zinc-binding metalloproteinase initially identified as a circulating protein in the serum of women during late pregnancy. In 2001, Bayes-Genis et al. [8] first reported PAPP-A as a promising marker for coronary artery disease (CAD) and acute coronary syndrome (ACS), observing significantly higher levels in unstable compared to stable

plaques. Subsequent studies have confirmed that elevated circulating levels of PAPP-A independently predict the risk of ischemic events. [9,10] The uncomplexed (active) form of PAPP-A is particularly elevated in ACS, where it acts as a metalloproteinase contributing to plaque rupture.

In the early stages of STEMI, PAPP-A seems to be a more sensitive marker of myocardial infarction than CKMB and troponin T. [11] Despite growing evidence of PAPP-A role in cardiovascular disease, its association with the clinical severity and risk stratification of NSTE-ACS remains uncertain. This study aims to clarify this relationship by examining serum PAPP-A levels in relation to clinical risk scores in patients with NSTE-ACS.

## 2. METHODS

### Study Population

This was a descriptive, cross-sectional observational study conducted in the Department of Biochemistry in collaboration with the Departments of General Medicine and Cardiology at SMS Medical College and Hospital, Jaipur, Rajasthan. A total of 100 age- and gender-matched subjects were enrolled based on predefined inclusion and exclusion criteria.

Patients presenting to the emergency department with chest pain and subsequently diagnosed with non-ST-elevation acute coronary syndrome (NSTE-ACS) by a trained cardiologist—based on clinical presentation, laboratory tests, and imaging findings—were included. The diagnosis of NSTE-ACS was established by the presence of typical chest pain lasting >20 minutes, along with ST-segment depression ≥0.1 mV and/or T-wave inversion in at least two contiguous leads on ECG.

Exclusion criteria included patients with coronary ectasia or structural abnormalities, coronary vasospasm, acute or chronic inflammatory diseases, malignancy, pregnancy, acute or chronic renal failure, myocarditis, or significant valvular heart disease.

### Clinical risk assessment

Clinical risk assessment of NSTE-ACS patients was conducted using the Thrombolysis in Myocardial Infarction (TIMI) risk score, which comprises seven independent predictors: age ≥65 years, presence of three or more traditional coronary artery disease risk factors (e.g., diabetes, hypertension, smoking, hyperlipidaemia, or family history), known coronary stenosis ≥50%, aspirin use within the past seven days, two or more anginal episodes in the preceding 24 hours, ST-segment deviation ≥0.5 mm on ECG, and elevated cardiac biomarker (Trop-T). Each variable contributes one point, resulting in a total score ranging from 0 to 7.

### Blood samples

Venous blood samples (5 mL) were collected aseptically into metal-free, anticoagulant-free tubes. After allowing the blood to clot for 20 minutes at room temperature, the samples were centrifuged for 15 minutes. The resulting serum was used for routine biochemical tests, with the remaining aliquots stored at −20°C, avoiding repeated freeze-thaw cycles. Routine biochemical parameters were analyzed using the Beckman Coulter AU 5100 system. Echocardiography was conducted using GE Vivid E9 machine, and electrocardiograms (ECG) were recorded with an Edan SE-1201 device. Serum PAPP-A levels were measured using the DRG PAPP-A ELISA kit following the manufacturer's protocol.

### Statistical analysis

All data were analyzed using SPSS version 26.0. Categorical variables were evaluated using the Chi-square test, while One-Way Analysis of Variance (ANOVA) was employed to compare means across the three cardiovascular risk groups. Where significant differences were observed, post hoc analysis was performed using the Bonferroni test. Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables as percentages. A p-value <0.05 was considered statistically significant.

## 3. RESULTS

A total of 100 participants were enrolled in the study and classified according to their clinical diagnosis. Of these, 34 (34.0%) were diagnosed with Non-ST-Elevation Myocardial Infarction (NSTEMI), and 66 (66.0%) with unstable angina. Demographic, clinical, and laboratory features of the patients are presented in Table 1.

The study population was stratified into three cardiovascular risk groups: low (n=46), intermediate (n=39), and high risk (n=15). The mean age increased significantly across the risk groups ($p < 0.001$), with high-risk participants being the oldest (66.07 ± 8.75 years). Although males predominated in all groups, the difference in gender distribution was not statistically significant ($p = 0.490$).

**Table 1. Baseline clinical, biochemical, and angiographic characteristics of the study population across cardiovascular risk categories**

| Variable | Low Risk (n = 46) | Medium Risk (n = 39) | High Risk (n = 15) | p-value |
|---|---|---|---|---|
| Clinical and Hemodynamic Data | | | | |
| Age (years) | 54.37 ± 10.72 | 63.05 ± 10.21 | 66.07 ± 8.75 | < 0.001 |
| Men, n (%) | 33 (71.74%) | 25 (64.10%) | 12 (80.00%) | 0.490 |
| Body mass index (kg/m²) | 27.56 ± 2.45 | 27.03 ± 2.20 | 27.44 ± 1.93 | 0.565 |
| Hypertension, n (%) | 11 (23.91%) | 15 (38.46%) | 9 (60.00%) | 0.033 |
| Diabetes mellitus, n (%) | 8 (17.39%) | 16 (41.03%) | 8 (53.33%) | 0.011 |
| Smoking (current), n (%) | 19 (41.30%) | 21 (53.85%) | 8 (53.33%) | 0.465 |
| Left ventricular ejection fraction (%) | 51.24 ± 9.02 | 48.05 ± 10.63 | 50.67 ± 8.63 | 0.302 |
| Biochemical and Hematological Data | | | | |
| Total cholesterol (mg/dL) | 178.65 ± 45.14 | 184.74 ± 50.08 | 170.33 ± 48.02 | 0.595 |
| LDL cholesterol (mg/dL) | 114.91 ± 38.77 | 106.53 ± 29.00 | 112.53 ± 27.29 | 0.516 |
| HDL cholesterol (mg/dL) | 53.22 ± 10.76 | 52.92 ± 9.43 | 49.47 ± 10.26 | 0.448 |
| Triglycerides (mg/dL) | 178.15 ± 119.19 | 171.92 ± 57.00 | 161.40 ± 53.22 | 0.820 |
| Creatinine (mg/dL) | 1.00 ± 0.21 | 0.96 ± 0.27 | 0.99 ± 0.28 | 0.797 |
| Random blood sugar (mg/dL) | 111.60 ± 68.61 | 132.17 ± 75.85 | 129.47 ± 54.04 | 0.367 |
| Hemoglobin (g/dL) | 13.41 ± 2.14 | 13.37 ± 2.27 | 12.10 ± 2.54 | 0.127 |
| PAPP-A(µg/mL) | 7.47 ± 8.46 | 6.02 ± 9.13 | 7.29 ± 9.23 | 0.738 |
| No. of diseased vessels, mean ± SD (n) | 1.04 ± 0.94 (46) | 2.05 ± 0.56 (39) | 2.73 ± 0.88 (15) | < 0.001 |

The number of diseased coronary vessels also increased significantly across risk groups (from 1.04 ± 0.94 in low-risk to 2.73 ± 0.88 in high-risk; $p < 0.001$). No significant differences were observed in BMI among the groups ($p = 0.565$). However, the prevalence of hypertension ($p = 0.033$) and diabetes mellitus ($p = 0.011$) was significantly higher in the medium and high-risk groups. Smoking status and left ventricular ejection fraction did not differ significantly across groups.

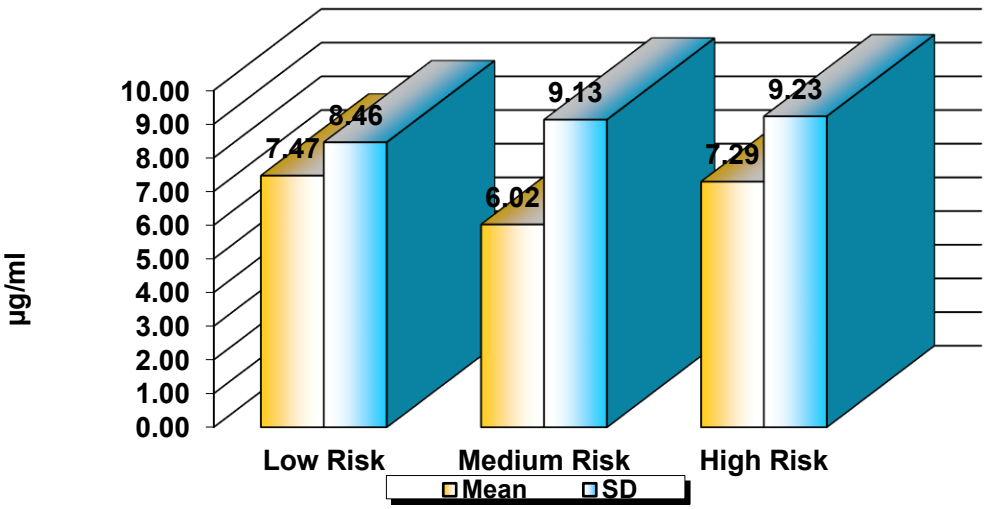


**Figure 1: Comparison of mean serum PAPP-A levels across cardiovascular risk groups**

As shown in Figure1 When serum PAPP-A levels were compared between the cardiovascular risk groups, it was found that the mean serum PAPP-A levels of low cardiovascular risk group were (7.47±8.46) followed by high-risk group (7.29±9.23) and medium risk group (6.02±9.13). When statistically analysed, all risk categories were found similar with respect to serum PAPP-A levels. (P=0.738)

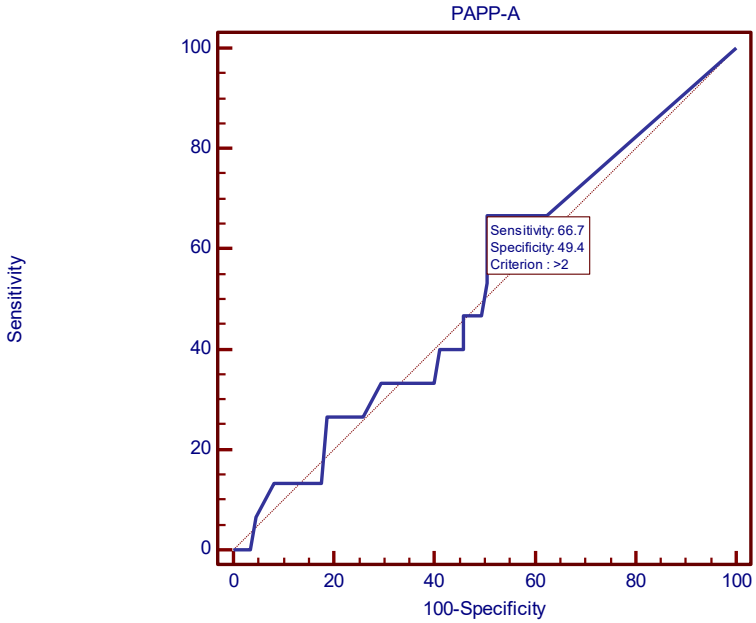


**Figure 2: ROC curve showing diagnostic performance of PAPP-A in identifying high cardiovascular risk in NSTE-ACS**

The ROC curve analysis for PAPP-A (figure 2) showed an Area Under the Curve (AUC) of 0.521, with a 95% confidence interval of 0.419 to 0.622 (P = 0.7919), indicating poor discriminatory ability. The optimal cut-off value was >2.0 µg/mL, corresponding to the highest Youden index. At this threshold, PAPP-A had a sensitivity of 66.67% (95% CI: 38.4 - 88.2%) and a specificity of 49.41% (95% CI: 38.4 - 60.5%). The positive likelihood ratio (+LR) was 1.32 (95% CI: 0.9 - 2.0) and the negative likelihood ratio (-LR) was 0.67 (95% CI: 0.3 - 1.4), suggesting limited diagnostic value.

## 4. DISCUSSION

Pregnancy-associated plasma protein-A (PAPP-A) is a zinc-binding metalloproteinase known to be abundantly expressed in plaque cells and the extracellular matrix of eroded and ruptured atherosclerotic plaques. [8] Its role as a potential biomarker for plaque instability and acute coronary syndromes has been well explored. However, in the present study, serum PAPP-A levels did not show a statistically significant difference across cardiovascular risk groups stratified by the TIMI score (P = 0.738). This indicates a lack of association between PAPP-A concentrations and clinical risk categories in patients with NSTE-ACS.

Despite its biological plausibility, PAPP-A demonstrated limited discriminatory performance in our cohort, with an AUC of 0.521, and modest sensitivity (66.67%) and specificity (49.41%) at the optimal cut-off value of >2.0 µg/mL. These findings suggest that PAPP-A may not be a reliable standalone biomarker for clinical risk stratification in NSTE-ACS patients. Our observations are consistent with previous studies. Heeschen et al. reported no significant difference in mean PAPP-A levels between patients with unstable angina (UA) and NSTEMI. [10] Similarly, a study by P. Gururanjan et al. found no significant variation in PAPP-A levels between NSTEMI and UA, although significantly higher levels were observed in STEMI cases. [12] This is further supported by Iversen et al. [11], who demonstrated that PAPP-A levels at admission were significantly elevated in STEMI patients compared to those with NSTEMI and UA.

In comparison to our findings, Laterza et al. reported an optimal PAPP-A cut-off of 0.22 mIU/L with similar sensitivity (66.7%) and specificity (51.1%), suggesting that while sensitivity remains modest across studies, specificity is consistently low. [13] Moreover, Lund et al. highlighted that PAPP-A rises early in STEMI and normalizes rapidly, especially in patients who undergo early reperfusion. [14] This raises an important consideration regarding the timing of sample collection, as PAPP-A may exhibit rapid kinetics that limit its utility in delayed presentations.

Taken together, our findings reinforce that while PAPP-A holds promise as a biomarker of plaque instability, its clinical

application in risk stratification for NSTE-ACS remains limited, particularly when used in isolation. Future research should focus on serial sampling at early time points and explore the combined use of PAPP-A with other biomarkers or imaging tools to enhance diagnostic and prognostic accuracy in acute coronary syndromes.

## 5. STUDY LIMITATIONS

This was a single-center observational study with a small sample size and uneven distribution across risk groups, which may limit statistical power. Clinical outcomes were not assessed; PAPP-A was analyzed only in relation to risk scores. As a hospital-based study, selection bias is possible, and findings may not be fully generalizable to the broader ACS population.

## 6. CONCLUSION

This study found no significant difference in serum PAPP-A levels across cardiovascular risk groups in NSTE-ACS patients. ROC analysis showed poor discriminatory ability, indicating that PAPP-A has limited value as a standalone marker for risk stratification. Further studies with larger cohorts and serial sampling are needed to assess its role in combination with other biomarkers.

## REFERENCES

[1] Prabhakaran D, Jeemon P, Roy A. Cardiovascular diseases in India: current epidemiology and future directions. Circulation. 2016 Apr 19;133(16):1605-20.

[2] Kipshidze N, Fareed J, Serruys PW, Moses J, editors. Textbook of interventional cardiovascular pharmacology. CRC Press; 2007 Jun 1.

[3] Rodriguez F, Mahaffey KW. Management of patients with NSTE-ACS: a comparison of the recent AHA/ACC and ESC guidelines. Journal of the American College of Cardiology. 2016 Jul 19;68(3):313-21.

[4] Chioncel O, Benson L, Crespo-Leiro MG, Anker SD, Coats AJ, Filippatos G, McDonagh T, Margineanu C, Mebazaa A, Metra M, Piepoli MF. Comprehensive characterization of non-cardiac comorbidities in acute heart failure: an analysis of ESC-HFA EURObservational Research Programme Heart Failure Long-Term Registry. European Journal of Preventive Cardiology. 2023 Sep;30(13):1346-58.

[5] Thorn EM, Khan IA. Pregnancy associated plasma protein-A: an emerging cardiac biomarker. Int J Cardiol 2007;117:370–2.

[6] Li X, Liu Q, Zhou T, Zhou S, Shou S. PAPP-A: a possible pathogenic link to the instability of atherosclerotic plaque. Med Hypotheses 2008;70:597–9.

[7] Consuegra-Sanchez L, Fredericks S, Kaski JC. Pregnancy-associated plasma protein-A (PAPP-A) and cardiovascular risk. Atheroscle rosis 2009;203:346–52.

[8] Bayes-Genis A, Conover CA, Overgaard MT, et al. Pregnancy associated plasma protein-A as a marker of acute coronary syn dromes. N Engl J Med 2001;345:1022–9.

[9] Lund J, Qin QP, Ilva T, et al. Circulating pregnancy-associated plasma protein A predicts outcome in patients with acute coro nary syndrome but no troponin I elevation. Circulation 2003; 108:1924–6.

[10] Heeschen C, Dimmeler S, Hamm CW, Fichtlscherer S, Simoons ML, Zeiher AM. Pregnancy associated plasma protein-A levels in patients with acute coronary syndrome: comparison with mark ers of systemic, inflammation, platelet activation and myocardial necrosis. J Am Coll Cardiol 2005;45:229–37.

[11] Iversen KK, Teisner AS, Teisner B, et al. Pregnancy-associated plasma protein A, a novel, quick and sensitive marker in ST segment myocardial infraction. Am J Cardiol 2008;101:1389–94.

[12] Priya Gururajan, Prema Gurumurthy, Nayar P, Srinivasa G, R. Sai Babu, A. Sarasabharati, et al. Pregnancy associated plasma protein-A (PAPP-A) as an early marker for the diagnosis of acute coronary syndrome. Indian Heart Journal. 2012 Mar 1;64(2):141–5.

[13] Laterza OF, Cameron SJ, Chappell D, Sokoll LJ, Green GB. Evaluation of pregnancy-associated plasma protein A as a prog nostic indicator in acute coronary syndrome patients. Clin Chim Acta 2004;348:163–9.

[14] Lund J, Qin Q, Ilva T, Nikus K, Eskola M, Porela P, et al. Pregnancy-associated plasma protein A: A biomarker in acute ST-elevation myocardial infarction (STEMI). Annals of Medicine. 2006 Jan;38(3):221–8.