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Original Article

Biochemistry Section

# Plasminogen Activator Inhibitor-1 Levels in Heart Failure Patients: A Cross-sectional Study

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## ABSTRACT

**Introduction:** Heart Failure (HF) is a worldwide health concern and a major cause of morbidity and mortality globally. Among the numerous biomarkers associated with HF, Plasminogen Activator Inhibitor-1 (PAI-1) has received attention for its role in poor fibrinolysis and thrombosis.

**Aim:** This study aimed to compare serum PAI-1 levels in patients diagnosed with HF to those of healthy participants.

**Materials and Methods:** This cross-sectional study was conducted in the Department of Biochemistry, in collaboration with the Department of Medicine at Sri Guru Ram Das Hospital, Amritsar, Punjab, India. The study comprised 50 individuals with confirmed HF from the inpatient department of the Medicine Department and 50 healthy individuals of comparable age, conducted from October 2019 to December 2023. Serum levels of PAI-1, N-terminal pro-B-type Natriuretic Peptide (NT-proBNP), Brain Natriuretic Peptide (BNP), creatinine, and Urine Albumin-to-Creatinine Ratio (UACR) were investigated and compared. The data were statistically analysed and presented as mean and standard deviation (SD). Odds ratio and Student's t-test were performed.

**Results:** The study included 100 participants, with a mean age of 62.3±10.4 years, comprising 68% males and 32% females, ensuring age and gender representation across both HF patients and healthy controls. The mean±SD of serum PAI-1 was 10.09±1.68 ng/mL in healthy individuals and 35.16±11.14 ng/mL in HF patients, indicating that PAI-1 could be a valuable indicator for diagnosing HF. A comparison with healthy controls showed significantly higher levels of PAI-1 ($p < 0.001$) in HF patients. PAI-1 had a significantly high odds ratio (OR) (585.8, 95% CI: 32.5-10554.5), showing a strong association. Furthermore, as the condition became more severe, the levels of these biomarkers increased significantly.

**Conclusion:** Serum levels of PAI-1 are significantly associated with HF, indicating that they could be used for the identification of HF. Further studies are required to validate these findings and evaluate the clinical benefit of targeting PAI-1 in HF management.


**Keywords:** Cardiovascular disease, Creatinine and albumin ratio, Fibrinolysis, Thrombosis

## INTRODUCTION

HF is a complicated cardiovascular condition characterised by the heart's inability to pump blood efficiently to meet the body's demands. It is a common and severe disorder that results in significant morbidity, mortality, and healthcare costs worldwide. Over the years, the global burden of HF has surged significantly, with the number of affected individuals increasing from 33.5 million in 1990 to over 64.3 million currently [1]. Approximately 500,000 new cases are diagnosed each year. Heart disease now accounts for 16% of all deaths worldwide [2]. The American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines classifies HF into three categories based on left ventricular ejection fraction (EF), which represents the amount of blood the heart pumps with each beat expressed as a percentage [3]:

1. HF with reduced EF (HFrEF): Defined as an EF of 40% or lower.
2. HF with preserved EF (HFpEF): Refers to EF levels of 50% or more.
3. HF with mid-range EF (HFmrEF): Categorised as EF levels between 40% and 49% [3].

This study evaluated the levels of PAI-1, BNP, NT-proBNP, and UACR in HF patients compared to healthy individuals to represent various pathophysiological pathways involved in the onset and progression of HF. BNP and NT-proBNP are natriuretic peptides released in response to the stretching of the heart muscle that occurs with Heart Failure (HF). They are considered gold-standard prognostic biomarkers [4]. The Urine Albumin-to-Creatinine Ratio (UACR) is the ratio of measured albumin to creatinine and is a key indicator of renal failure [5]. Elevated UACR may also be related to increased Left Ventricular (LV) mass and is associated with right ventricular remodeling [6]. By estimating BNP and NT-proBNP, we can follow a reliable path, and UACR will add to the understanding of pathophysiology. However, the focus of our study was mainly on PAI-1 estimation, as it is not extensively explored and may contribute to HF.

Nearly forty years ago, PAI-1 was discovered for the first time as an inhibitor of the fibrinolytic system associated with cultured bovine endothelial cells [7,8]. Shortly after, multiple types of research confirmed the presence of PAI-1 in human plasma [9-11], as well as in various other cell types throughout the body, including the liver, spleen, lungs, kidneys, and adipocytes, although concentrations and functional activities varied across these different tissues [12-17]. PAI-1 is an important component of the fibrinolytic system that regulates the balance of clot production and disintegration. Emerging data suggest that PAI-1 may contribute to the pathophysiology of HF, making it an appealing target for future research [14]. Endothelial cells produce PAI-1, which inhibits tissue-type Plasminogen Activator (tPA) to reduce the fibrinolytic process. Under pathological circumstances, pro-inflammatory substances can upregulate PAI-1 production, inducing a pro-thrombotic state. The significance of high PAI-1 levels in HF patients has yet to be determined [17].

These biomarkers were assessed in this study as they represent different aspects of HF pathophysiology, including inflammation, fibrosis, cardiac stress, and endothelial dysfunction. By measuring these biomarkers, the study aimed to contribute to a more comprehensive understanding of HF mechanisms, especially in the Indian population, where such data is lacking. Most studies have focused on general cardiovascular risks or lacked data on PAI-1 variations across HF subtypes (HFpEF, HFmrEF, HFrEF) and its

correlation with severity [18-21]. This study addresses these gaps by evaluating PAI-1 levels in HF patients compared to healthy controls, exploring subtype-specific variations, and assessing its diagnostic and prognostic utility, thereby providing novel insights into its clinical relevance and therapeutic potential. With this background, the present study was conducted to compare serum PAI-1 levels in patients diagnosed with HF to those in healthy participants.

## MATERIALS AND METHODS

This cross-sectional study was conducted in association with the Department of Medicine at Sri Guru Ram Das Hospital, Amritsar, by the Department of Biochemistry at the Sri Guru Ram Das Medical Institute of Science and Research, Amritsar, from October 2019 to December 2023. Every participant granted informed consent before their blood samples were collected. The participants were taken from the Outpatient Department (OPD) and Inpatient Departments (IPD) of Sri Guru Ram Das Hospital, Amritsar, affiliated with the Sri Guru Ram Das Medical Institute of Science and Research, Amritsar. The Institutional Research and Ethics Committee (IEC No: Patho 690/19; dated 21.10.2019) granted clearance before the study could be carried out.

**Inclusion criteria:** The research comprised patients with hypertension, Coronary Artery Disease (CAD), Diabetes Mellitus (DM), left ventricular (LV) dysfunction, or a history of dyspnea who presented to the OPD/IPD. Patients with HF were classified using the American Heart Association's guidelines [3]. Hence, the diagnosis of HF was made according to established guidelines: patients diagnosed with an EF less than 50% and high blood pressure (systolic BP≥140 mm Hg or diastolic BP≥90 mm Hg) were considered for participation as cases [3]. Normal healthy individuals with no personal or family history of HF were included as controls.

**Exclusion criteria:** The study excluded patients with a history of inflammatory diseases, cancer, obesity, Recurrent Pregnancy Loss (RPL), or pre-eclampsia. These conditions were specifically excluded since they have been shown to elevate PAI-1 levels, which may interfere with the analysis of the targeted biomarker in this investigation. By excluding these conditions, the study aimed to achieve more accurate and reliable results for biomarkers linked with HF.

**Sample size:** Collet JP et al. compared serum levels of PAI in HF patients and found that serum PAI-1 levels were significantly higher (24.8±10.1 ng/mL) in HF individuals compared to non-HF individuals (1.1±3.3 ng/mL) with a p-value of 0.004 [22]. This data was used in the following formula to calculate the sample size:

(Za2+ZB)2

(SD2)/d2

n=Sample size

Za2=Z value at 5% error (1.96)

Z\beta=Z value at 10% (1.28)

SD=average standard deviation of HF individuals as compared to healthy (SD1+SD2)/2

d=effect size

The above values were entered in G Power version 3.1 software. The software calculated the sample size for HF individuals and healthy groups to be 49. The study included a total of 100 individuals, comprising 50 HF patients (with 17, 19, and 14 patients with HFrEF, HFmrEF, and HFpEF, respectively) considered as cases. As a control group, 50 healthy, age-matched members of the general population were selected.

### Study Procedure

**Sample collection:** Patients' histories were collected, and each case underwent a thorough clinical investigation following a predefined protocol. Data on age, gender, family history of HF, and any other complications were recorded. A 2mL blood sample was drawn by venipuncture under aseptic conditions. Routine investigations were carried out in every case. Blood samples were taken from both HF patients and healthy controls, and the levels of serum PAI-1, BNP, NT-proBNP, and UACR were evaluated and compared. The estimation of serum PAI-1 was carried out using an ELISA reader (Erba Lisa Scan II) [23]. BNP and NT-proBNP levels were measured using a two-site sandwich immunoassay [24]. The UACR was determined by dividing the measured concentration of albumin (in mg/L) by the creatinine concentration (in g/L) in the urine sample. The result is expressed in milligrams of albumin per gram of creatinine (mg/g), allowing for standardized comparison and clinical interpretation [25].

(UACR using formula=microalbumin(mg/dL)×100)

Creatinine (g/dL)

The results were automatically calculated by the Dimensions RXL chemistry analyzer (Siemens), with parameter results quoted in units of pg/mL.

The biological reference ranges for the parameters assessed is given in [Table/Fig-1].

| Parameters | Normal levels | High levels |
|---|---|---|
| PAI-1 | 5-20 ng/mL | >20 ng/mL |
| BNP | <100 pg/mL | >100 pg/mL |
| NT-proBNP | <125 pg/mL | >125 pg/mL |
| UACR | <17 mg/g | >17 mg/g |

**[Table/Fig-1]:** Biological reference interval.

## STATISTICAL ANALYSIS

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) software version 21.0 (SPSS Inc., USA). The data for biochemical analysis are expressed as mean and standard deviation (SD). Student's t-test was used for statistical comparisons. An unpaired t-test was employed to find significant differences between the two groups. The odds ratio (OR) was calculated to determine the association between these groups. A p-value of ≤0.05 was defined as statistically significant.

## RESULTS

The study included 100 participants, with a mean age of 62.3±10.4 years. The case group (n=50) consisted of HF patients, while the control group (n=50) comprised healthy individuals. Gender distribution was similar across groups, with an overall 68% of participants being male and 32% female. The age range in the control group was 43-77 years, while in the case group it was 45-85 years, indicating comparable demographic representation.

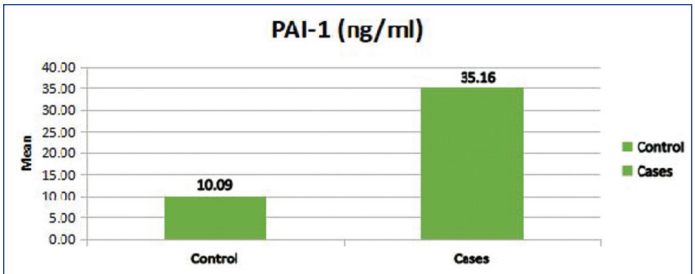
[Table/Fig-2] demonstrates different variables across the various classes of HF. The age distribution in the control group suggests that the case group had greater variability and an increased mean age compared to the control group. The highest male percentage was observed in the HFpEF group, at 76.5%. The p-value of 0.874 indicates no significant variation in gender distribution among HF classes. The HFmrEF group had the highest mean age (63.18±10.49 years) and BNP levels (366.18±41.39 pg/mL), whereas the HFpEF group included a greater percentage of men (76.5%). The HFrEF group had significantly higher PAI-1 levels (43.92±6.66 ng/mL) and NT-proBNP levels (1337.56±77.72 pg/mL). Furthermore, the HFmrEF group exhibited the highest UACR, indicating severe renal impairment (124.82±91.63 mg/g). The control group had a mean age of 55.96±8.54 years, with 76% male and 24% female.

Biomarker levels in the control group, such as PAI-1 (10.09±1.68 ng/mL), BNP (55.18±14.95 pg/mL), NT-proBNP (93.34±17.49 pg/mL), and UACR (7.92±3.65 mg/g), were within normal ranges, indicating the participants' healthy physiological status and providing a baseline for comparison with HF patients.

| Varaibles | | HFpEF | | HFmrEF | | HFrEF | | p-value | Control | | p-value (cases vs control) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Mean | SD | Mean | SD | Mean | SD | | Mean | SD | |
| Age (years) | | 56.18 | 10.32 | 63.18 | 10.49 | 62.13 | 9.27 | 0.126 | 55.96 | 8.54 | 0.24 |
| Gender | Male (%age) (frequency) | 76.5% (13) | - | 70.6% (12) | - | 68.8% (11) | - | 0.874 | 76% (38) | | 0.628 |
| | Female (%age) (frequency) | 23.5% (4) | - | 29.4% (5) | - | 31.3% (5) | - | | 24% (12) | | |
| PAI-1 (ng/ml) | | 21.22 | 2.95 | 40.86 | 3.54 | 43.92 | 6.66 | <0.001* | 10.09 | 1.68 | <0.001* |
| BNP (pg/mL) | | 90.76 | 24.53 | 366.18 | 41.39 | 359.63 | 39.18 | <0.001* | 55.18 | 14.95 | <0.001* |
| NT pro-BNP (pg/mL) | | 183.24 | 54.88 | 1327.76 | 97.99 | 1337.56 | 77.72 | <0.001* | 93.34 | 17.49 | <0.001* |
| UACR (mg/g) | | 26.47 | 4.76 | 124.82 | 91.63 | 102.88 | 58.55 | <0.001* | 7.92 | 3.65 | <0.001* |

**[Table/Fig-2]:** Comparison of variables in different types of Heart Failure (HF).
(*significant at p<0.001)

[Table/Fig-3] shows a significant difference in PAI-1 levels between the control and case groups. The mean PAI-1 level in the control group was within the normal range; however, in the case group, it was significantly higher at 35.16 ng/mL (SD=11.14), with a p-value of 0.001, suggesting strong statistical significance. The study demonstrates that all parameters—PAI-1, BNP, NT-proBNP, and UACR—are strongly associated with the results (p-value <0.001).




**[Table/Fig-3]:** Comparison of mean Plasminogen Activator Inhibitor-1 (PAI-1) (ng/mL) levels between control and case groups.

PAI-1 has a significantly high OR (585.8, 95% CI: 32.5-10554.5), while BNP (576.00, 95% CI: 77.9-4257.8) and NT-proBNP (2160.00, 95% CI: 131.14-35575.02) show robust connections but have broad confidence intervals, indicating variability in their estimations. The UACR (13.93, 95% CI: 5.4-35.8) indicates an association with a smaller confidence interval (CI). Overall, these characteristics are extremely important predictors, although variability in certain estimations needs additional investigation. These results highlight the potential role of PAI-1 as a biomarker of HF [Table/Fig-4].

| Parameters | Odds Ratio (OR) (95% CI) | Z-value | p-value |
|---|---|---|---|
| PAI-1 | 585.8 (32.5 to 10554.5) | 4.320 | 0.001* |
| BNP | 576.00 (77.9 to 4257.8) | 6.28 | 0.001* |
| NT pro-BNP | 2160.00(131.14 to 35575.02) | 5.372 | 0.001* |
| UACR | 13.93 (5.4 to 35.8) | 5.46 | 0.001* |

**[Table/Fig-4]:** Association of PAI-1 levels between Heart Failure (HF) patients and controls.
(*Significance level p<0.001)

## DISCUSSION

In this research, the levels of PAI-1 were examined in different categories of HF patients—specifically, those with pEF, mrEF, and rEF—and compared to healthy controls. Our findings demonstrate a statistically significant increase in PAI-1 levels (p<0.001) among HF patients compared to healthy individuals. The results suggest that serum PAI-1 levels are significantly elevated in HF patients when compared with those of healthy individuals, particularly showing the highest rise in HFrEF patients. This supports the hypothesis that PAI-1, as a regulator of fibrinolysis, plays a critical role in the pathophysiology of HF. The progressive increase in PAI-1 levels from HFpEF to HFrEF patients may reflect the severity of cardiac dysfunction and the associated pro-thrombotic state [17, 26]. Elevated PAI-1 levels in HFrEF patients could be attributed to greater endothelial dysfunction and systemic inflammation, which are known to worsen HF [27,28].

Our study aligns with previous research that has demonstrated elevated PAI-1 levels in HF patients. For instance, one study found that patients with PAI-1 activity greater than 3.7 U/mL had significantly higher mortality (p<0.001), suggesting that this increase in PAI-1 might lead to HF development [29]. Similarly, another study indicated that polymorphisms in the PAI-1 gene, as well as components of metabolic syndrome in CAD, might serve as biomarkers for CAD treatment and diagnosis [30]. Another piece of research observed that elevated plasma PAI-1 antigen levels are associated with Major Adverse Cardiovascular Events (MACE), with an OR of 1.91 and a 95% CI of 1.18-3.24 [17].

A similar investigation discovered several fibrinolytic factors that had received little attention in HF, including PAI-1, tPA, urokinase-type PA (uPA), and soluble urokinase PA surface receptor (suPAR). While they found that tPA concentrations were not associated, longitudinally observed PAI-1, uPA, and suPAR levels were highly correlated with adverse cardiac events in patients with chronic HF from the Bio-SHiFT study [31]. Winter and his colleagues reported that the tPA/PAI-1 complex concentration provided additional prognostic value beyond that of NT-proBNP, identifying it as an independent predictor of all-cause and cardiovascular mortality in patients with HF with pEF [32]. On the other hand, another study did not find the association; they evaluated that PAI-1 levels were 3.80±2.86 ng/mL, with a median of 2.71, an interquartile range (IQR) of 1.86-5.14, and a range of 0.54-16.93 ng/mL. PAI-1 showed 7.35% inter-assay and 4.85% intra-assay variability, with a lower detection limit of 0.3 ng/mL. When measured for endothelial dysfunction, PAI-1 could not establish an association with the condition directly [33].

Biomarkers like PAI-1, BNP, NT-proBNP, and UACR may offer insights into the pathophysiology, diagnosis, and prognosis of HF. BNP and NT-proBNP are well-established diagnostic biomarkers for HF [34,35]. UACR is indicative of kidney damage [5] and endothelial dysfunction [6], and it is associated with cardiac remodeling. Higher UACR levels correlate with an increased risk of mortality and HF hospitalisations [6,36]. PAI-1, which is associated with adverse outcomes due to fibrosis and remodeling processes, could provide additional diagnostic value [26-28]. While BNP and NT-proBNP are primarily the gold standards used for diagnosing and prognosticating HF [37], PAI-1 and UACR could add more information about the underlying mechanisms and risk stratification.

Among all the established and emerging biomarkers considered in our study, PAI-1 has demonstrated the most prominent results. Most studies report a similar trend to our findings, highlighting the potential role of PAI-1 as a biomarker for HF. However, our study provides additional information through a comparative analysis across different classes of HF, offering more insight into how PAI-1 levels vary with the type of HF. It has been noted that PAI-1 levels are higher in HFrEF than in HFpEF.

### Limitation(s)

The relatively small sample size and demographic characteristics that may not reflect the broader population could limit the applicability and generalisability of the findings. Medication and co-morbidities

were omitted, which may lead to unaccounted confounding factors. Future studies should include more diverse cohorts, comprehensive clinical profiles, larger samples, and explore longitudinal changes in PAI-1 levels to better understand their role in HF progression.

## CONCLUSION(S)

In HF, several biological mechanisms, including the fibrinolytic system, are activated. Our study indicates that when HF patients are compared with healthy individuals, the extent of fibrinolytic cascade upregulation is linked to adverse events, leading to significantly increased levels of serum PAI-1. In conclusion, PAI-1 levels could be used to detect HF and its severity. More research is needed to validate these findings and investigate their clinical implications.

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