

# Procalcitonin and D-dimer in Predicting the Severity of Congestive Heart Failure

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## Abstract

**Background:** Congestive heart failure (CHF) is an intricate clinical syndrome that significantly contributes to morbidity and mortality. Despite extensive advancements, research on markers of severity in CHF remains scarce.

**Objectives:** This study aims to evaluate procalcitonin (PCT) and D-dimer as severity predictors in CHF.

**Methods:** CHF patients were included in this retrospective single-center study between January to December 2022. The population group was randomized and classified as stages I to IV based on the New York Heart Association (NYHA) functional classification system. Mean differences and multivariate analysis were performed with a statistical significance at  $p < 0.05$ .

**Results:** A total of 72 CHF patients were included in the study. The correlation analysis revealed that PCT ( $p \leq 0.001$ ), D-dimer ( $p \leq 0.001$ ), and systolic blood pressure (SBP) ( $p = 0.005$ ) were all found to be correlated to the CHF stages. In the analysis of mean differences, PCT ( $p < 0.001$ ) and D-dimer ( $p < 0.001$ ) showed significant variation across the CHF stages. The optimal PCT and D-dimer cut-off values were 1.190 ng/mL and 2.110 ng/mL respectively. Conversely, the area under the receiver operating characteristic (ROC) curve was significant for both PCT (Area Under the Curve [AUC]: 0.962; 95% CI: 0.921-1.000;  $p < 0.001$ ) and D-dimer (AUC: 0.929; 95% CI: 0.868-0.989;  $p < 0.001$ ). Meanwhile, through multivariate analysis, D-dimer is significantly correlated with the various CHF stages (95% CI: 0.034-0.101,  $p < 0.001$ ) but not for PCT (95% CI: 0.009-0.017,  $p = 0.561$ ).

**Conclusion:** A significant association between D-dimer levels and CHF stages was found, suggesting the potential of D-dimer as a valuable marker of severity in CHF patients.

## Introduction

Heart failure (HF) is a multifaceted condition characterized by the failure of the heart to maintain the demands imposed on it, often resulting in pump failure and fluid buildup.<sup>1</sup> HF affects an estimated 64.3 million individuals globally.<sup>2</sup> According to a meta-analysis conducted based on echocardiographic screening studies, the prevalence of HF in individuals aged 65 years and over is approximately 11.8 percent. This would result in a projected prevalence of 4.2 percent in the general population.<sup>3</sup> According to a recent study that included 1.25 million individuals, there is a 5% probability of developing

HF throughout the rest of life by the age of 30.<sup>4</sup> The main risk factors of HF include diabetes, hypertension, family history of heart disease, obesity, and chronic infection.<sup>5</sup> Both left-side and right-side malfunction of the heart has a significant impact on the clinical presentation of HF. As a result of left ventricular dysfunction, pulmonary pressure rises, causing pulmonary congestion, dyspnea, and tachypnea.<sup>6</sup> Renal dysfunction, peripheral malperfusion, and nutritional malabsorption with indications of cardiac cachexia emerge as peripheral circulation is diminished. The permanent activation of neurohumoral systems in a chronic state leads to increased organ volume overload, peripheral vasoconstriction, increased heart rate, and further deterioration of the cardio-renal system.<sup>7,8</sup> Congestive heart failure (CHF) is classified, based on the severity of symptoms and results of physical exams, into groups I, II, III, and IV.<sup>9</sup> Therefore, accurate diagnosis and effective treatment are imperative in order to minimize recurrent hospital admissions, enhance the overall quality of life, and optimize patient outcomes. One approach in this regard entails conducting comprehensive laboratory analyses, which serve to elucidate the etiology and/or severity of CHF. A wide array of cardiac-specific tests and prognostic variables, distinguished by their exceptional sensitivity and specificity, have been extensively employed for this purpose.<sup>10</sup>

## Keywords

Heart Failure; Procalcitonin; Severity of Illness Index

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**Central Illustration: Procalcitonin and D-dimer in Predicting the Severity of Congestive Heart Failure**


## PROCALCITONIN AND D-DIMER IN PREDICTING THE SEVERITY OF CONGESTIVE HEART FAILURE

|              | NYHA CLASS |       |       |        |        |
|--------------|------------|-------|-------|--------|--------|
|              | I          | II    | III   | IV     | P      |
| MEAN PCT     | 0.533      | 2.255 | 3.691 | 63.752 | <0.001 |
| MEAN D DIMER | 1.245      | 1.845 | 4.497 | 22.853 | <0.001 |

### PROCALCITONIN

**CUT OFF VALUE**  
1.190

**AUC [95%CI]**  
0.962 (0.921 - 1.000)

**MULTIVARIATE ANALYSIS**  
P = 0.561

### D-DIMER

**CUT OFF VALUE**  
2.110

**AUC [95%CI]**  
0.929 (0.868 - 0.989)

**MULTIVARIATE ANALYSIS**  
P < 0.001

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NYHA: New York Heart Association; PCT: procalcitonin; AUC: Area Under the Curve.

The natural course of CHF also influences the inflammatory and immune systems. Procalcitonin (PCT), a pro-peptide derived from calcitonin, has been extensively investigated for its clinical benefits for individuals with CHF. Although serum PCT lacks specificity for infections, patients with HF may experience an elevation in its levels due to intestinal endotoxin resorption induced by CHF.<sup>11</sup> The simplicity of conducting PCT assays, particularly in basic care settings, confers advantages in employing it as a diagnostic and prognostic biomarker for the early identification and staging of CHF. Numerous studies have implicated serum PCT levels as promising HF biomarkers, given their notable sensitivity and specificity in diagnosing, assessing the severity of, and predicting a poorer prognosis in CHF patients.<sup>12</sup> Patients suffering from HF are at an increased likelihood of encountering thromboembolic events within the vascular system and experiencing coagulation abnormalities. As a biomarker indicative of hemostatic disorders and thrombosis, D-dimer levels can be assessed in cases of CHF. Multiple studies have underscored the benefits of measuring D-dimer levels in risk stratification of elderly hospitalized CHF patients.<sup>13</sup> Elevated D-dimer levels have been correlated with heightened mortality risk in CHF patients, signifying their potential role as an indicator for intensifying medication interventions. D-dimer exhibits a

significant promise as a valuable prognostic marker for CHF due to its predictive capabilities surpassing those of established prognostic markers.<sup>14</sup>

Despite the individual associations of PCT and D-dimer with the onset and incidence of HF, their potential significance in prognosticating the severity in CHF patients has been relatively understudied. Consequently, the objective of this investigation is to assess the possible role of PCT and D-dimer in predicting the severity of CHF patients receiving treatment.

## Methods

### Study design and study participants

This retrospective cross-sectional study was conducted at a single center and approved by the Ethics Committee of Sanglah General Hospital, in Bali, Indonesia, which is affiliated with Udayana University. Data for the study was obtained from the medical records of 72 CHF patients admitted to the hospital. Patients were selected using stratified random sampling from January 2022 to December 2022. Stratified random sampling was employed to ensure that the study sample accurately represented the diverse population of CHF patients treated at the hospital during this period. Stratified random sampling

was employed to ensure that the study sample accurately represented the diverse population of CHF patients treated at the hospital during this period. Patients were stratified based on three key variables: New York Heart Association (NYHA) functional classification (Class I-IV), age groups ( $\leq 50$  years, 51-70 years,  $> 70$  years), and sex (male, female). The proportional allocation method was used to determine the number of patients to be selected from each stratum, corresponding to the proportion of each subgroup in the overall CHF patient population at the hospital during the study period. From the total sample, a sample size of 72 patients was determined using a margin of error of 5%, a confidence level of 95%, and a power of 80%. Once the population was stratified, patients were randomly selected from each stratum using a computer-generated randomization process in order to reduce selection bias. This stratified approach allowed for a more precise evaluation of how PCT and D-dimer levels correlate with CHF severity across different patient subgroups.

The diagnosis of CHF in this study was based on specific criteria and diagnostic parameters. CHF diagnosis primarily relied on clinical manifestations and was confirmed through a combination of clinical, laboratory, and imaging assessments. CHF diagnosis involved the following criteria: (1) Clinical symptoms: patients presented with characteristic symptoms, such as dyspnea, fatigue, fluid retention (edema), and evidence of poor tissue perfusion; (2) Radiological assessment: chest X-rays were used to identify pulmonary congestion and assess cardiac silhouette enlargement; (3) Echocardiography: echocardiographic evaluation was performed to assess cardiac structure and function, including left ventricular ejection fraction (LVEF). CHF is defined as an impairment in ventricular filling or blood ejection into the systemic circulation due to a structural or functional cardiac condition, further diagnosed and classified based on NYHA criteria. NYHA classification was made based on the presenting symptoms of patients.

Inclusion criteria for the study encompassed individuals aged 18 years or older who received a confirmed diagnosis of CHF based on specific clinical criteria, including characteristic symptoms, radiological assessments, and echocardiography. Exclusion criteria excluded individuals under the age of 18 years and those with a history of malignancy, deep vein thromboembolism, suspected or confirmed pulmonary thromboembolism, recent surgery, or recent trauma (within the past month) that may elevate D-dimer levels. Furthermore, to minimize potential bias when using the PCT level parameter, the study excluded patients with active infections (bacterial, parasitic, or fungal) undergoing antibiotic treatment, individuals with noninfectious systemic inflammatory responses, and those with end-stage renal failure. These stringent criteria were implemented to ensure a more homogeneous patient population for analysis and to maintain the integrity of the objectives of the study.

### Data collection and imputation

Prior to treatment initiation, data entry was conducted based on predetermined variables. An electronic medical record system was used to extract demographic information, vital signs, clinical characteristics, laboratory test results, and outcomes of patients upon admission and throughout

their hospitalization. The initial laboratory test results after admission, including blood tests for routine examination, PCT, D-dimer, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), random blood glucose, creatine, PPT, and APPT, were collected. The quantitative latex turbidimetric test was used to quantify the D-dimer level, and a cutoff value of 0.5  $\mu\text{g/mL}$  was determined to be within the normal range. PCT level is determined quantitatively using a chemiluminescent microparticle immunoassay method, with a result of 0.15  $\text{ng/mL}$  being regarded within the normal range. Clinical manifestations of patients were assessed and classified according to the NYHA functional classification, as shown below: (1) NYHA Class I (Mild): An individual exhibits no discernible symptoms of HF during routine physical activity. This individual can partake in normal activities without encountering excessive fatigue, palpitations, or dyspnea. Any symptoms that may manifest are typically limited to strenuous exercise. (2) NYHA Class II (Mild to Moderate): Patients classified as NYHA Class II present with mild to moderate HF symptoms. The individual remains comfortable at rest or during light exertion but may experience fatigue, palpitations, or shortness of breath when engaging in more physical activities. Their ability to perform everyday tasks remains largely unaffected. (3) NYHA Class III (Moderate): This stage is characterized by pronounced limitations in physical activity. The patient experiences comfort while at rest, but any level of exertion beyond basic daily activities can elicit symptoms like fatigue, palpitations or dyspnea. (4) NYHA Class IV (Severe): NYHA Class IV designates the most severe manifestation of HF symptoms. An individual in this category is unable to engage in any form of physical activity without experiencing discomfort. Symptoms persist even during periods of rest, and even minimal exertion exacerbates their condition. Patients in this stage often endure severe fatigue, palpitations, and dyspnea even when at rest.

Experienced physicians and statisticians reviewed and verified the data. Missing data were imputed using SPSS (version 25) software through regression imputation after excluding variables with excessive missing values ( $> 20\%$ ). The reliability of the imputed data was evaluated by comparing the baseline data before and after imputation.

### Study outcomes and statistical analysis

Statistical analyses were performed using version 25 of the Statistical Package for the Social Sciences (SPSS) developed by SPSS Inc. in Chicago, IL, USA. Continuous variables are presented as mean  $\pm$  standard deviation (SD) for normally distributed data or as median and interquartile range (IQR) for non-normally distributed data. In contrast, categorical variables are expressed as absolute and relative frequencies. The normality of data distribution was assessed using the Kolmogorov-Smirnov test. The correlation between research variables and the HF stage was assessed using Pearson Correlation for normally distributed data and the Spearman Rho Test for data not conforming to a normal distribution. To investigate the significance of PCT and D-dimer concerning the HF stages, ANOVA tests were employed, followed by a Mann-Whitney test with Bonferroni corrections. Any  $p$ -value less than 0.0083 would be considered statistically significant

after Bonferroni correction. To discern the relationship between the independent and dependent variables, a multivariate regression linear test was conducted after all necessary assumptions were met. Optimal cutoff values for these variables were determined via Receiver Operating Characteristic (ROC) analysis, while the Area under the Curve (AUC) was determined through multivariate analysis levels. The cutoff point for the ratio was identified using the ROC curve. The predetermined threshold for statistical significance was established at  $p < 0.05$ .

#### Ethical approval

The study was conducted in accordance with the International Conference on Harmonization – Good Clinical Practice (ICH-GCP) and approved by the Ethics Committee of the Faculty of Medicine of Udayana University, in Bali, Indonesia (972/UN14.2.2.VII/14/LT/2022).

## Results

#### Baseline Characteristics and Correlation Analysis of Variables

This study was conducted as an observational analytical research with a cross-sectional design. The aim of the study was to assess the mean differences in PCT and D-dimer levels across various HF stages and to investigate the correlation between the research variables and the HF stages in patients being treated at Prof. Dr. I.G.N.G. Ngoerah General Hospital. From January 2022 to December 2022, a total of 72 research samples were included in this study.

Based on the baseline characteristics shown in Table 1, the research cohort predominantly comprised male subjects. The median blood pressure profiles of the participants demonstrated lower-than-normal systolic and diastolic pressures. Notably, both SGOT and SGPT levels were elevated. The normality of the data was assessed using appropriate statistical tests. Variables that displayed a  $p$ -value  $< 0.05$  in the normality tests were identified as non-normally distributed. Consequently, specialized analytical methods appropriate for non-normally distributed data will be employed in subsequent analyses. Correlation analysis was performed to investigate the relationship between the research variables and the HF stages. The results of the correlation analysis provided insights into the associations between the research variables and the HF stages. Based on the analysis, significant correlations were found between the variables of PCT levels, D-dimer levels, and systolic blood pressure (SBP).

#### Analysis of Mean Differences of Independent Variables on the HF Stages

Based on the analysis of mean differences, the results are shown in Table 2. The analysis revealed significant mean differences in the variables of PCT and D-dimer across different HF stages. In order to elucidate the specific stages that exhibit significant differences in mean PCT and D-dimer levels, a comprehensive post-hoc analysis was performed, as depicted in Table 3. The results of the post-hoc analysis

revealed noteworthy variations in mean PCT levels between stages I and III, stages I and IV, stages II and IV, and stages III and IV. Based on the post-hoc analysis, significant differences in mean D-dimer levels were found between stages I and III, stages I and IV, stages II and III, and stages III and IV.

#### Analysis of ROC Variables PCT and D-Dimer on the HF Stages

In order to ascertain the optimal cutoff points of PCT and D-Dimer levels in relation to the HF stages, a ROC analysis was performed on the variables of PCT and D-Dimer (Figure 1). Based on the ROC analysis, the cutoff point for the PCT level was determined to be 1.190, while the cutoff point for D-Dimer was found to be 2.110. In addition to the cutoff points, the ROC analysis also yielded an AUC of 0.962 for PCT and 0.929 for D-Dimer, both with a  $p$ -value of less than 0.001 (Table 4).

#### Multivariate Analysis of the Influence of Research Variables on the HF Stages

A comprehensive multivariate analysis using linear regression was performed to evaluate the independent correlation of the explanatory variables with the dependent variable. The results are shown in Table 5, offering insights into the collective impact of these variables on the HF stages. By considering the interrelationships and interactions between the independent variables, the multivariate analysis provides valuable insights into the collective impact of these variables on the outcome of interest. Based on the analysis results, a significant finding was observed for the D-dimer variable.

## Discussions

The role of PCT and D-dimer in CHF surpasses their conventional applications as markers of infection and coagulation. Elevated PCT levels in CHF patients can be attributed to systemic inflammation and bacterial translocation due to mesenteric congestion, a common phenomenon in advanced HF. This inflammation, driven by cytokines and endotoxins, underscores the relationship between immune activation and cardiac dysfunction. Similarly, the rise in D-dimer levels is indicative of heightened fibrinolytic activity, a response to the prothrombotic state often seen in CHF. This state is exacerbated by chronic inflammation, endothelial dysfunction, and neurohormonal activation, which collectively contribute to thromboembolic events in HF patients. Understanding these mechanisms is crucial, as they provide insight into how PCT and D-dimer levels reflect the pathophysiological severity of CHF, thus reinforcing their potential as prognostic markers.

#### PCT

PCT is a polypeptide precursor of the hormone calcitonin, which is primarily produced by the C-cells of the thyroid gland under normal physiological conditions. Multiple studies have shown that inflammation plays a central role in the pathophysiology of severe HF.<sup>15-17</sup> During systemic inflammation, particularly in the context of bacterial infections,

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**Table 1 – Baseline characteristics, normality test, and correlation analysis.**

| Variables                    | Value/ Frequency      | Normality test | Correlation analysis with HF stage |                       |
|------------------------------|-----------------------|----------------|------------------------------------|-----------------------|
|                              |                       |                | Correlation Coefficient            | P-value               |
| Age (years)                  | 54 [46–62]            | 0.031          | 0.039                              | 0.746 <sup>b</sup>    |
| Gender                       |                       |                |                                    |                       |
| Male                         | 42 (58.3%)            |                |                                    |                       |
| Female                       | 30 (41.6%)            |                |                                    |                       |
| PCT (ng/mL)                  | 8.079 [0.02-156.09]   | 0.035          | 0.739                              | < 0.001 <sup>*b</sup> |
| D-Dimer (mg/L)               | 5.191 [0.02-45.98]    | 0.021          | 0.638                              | < 0.001 <sup>*b</sup> |
| Heart Rate (x/min)           | 82 [65 – 142]         | 0.042          | -0.138                             | 0.250 <sup>b</sup>    |
| Blood Tension (mmHg)         |                       |                |                                    |                       |
| Systole                      | 107 [80 – 138]        | 0.029          | -0.327                             | 0.005 <sup>*b</sup>   |
| Diastole                     | 74 [63 – 92]          | 0.018          | -0.201                             | 0.092 <sup>b</sup>    |
| SGOT (UI/L)                  | 68.15 [34.45 – 92.64] | 0.035          | 0.193                              | 0.106 <sup>b</sup>    |
| SGPT (UI/L)                  | 43.68 [12.32 – 82.79] | 0.021          | 0.030                              | 0.806 <sup>b</sup>    |
| Random Blood Glucose (mg/dL) | 135.436 ± 72.042      | 0.88           | -0.213                             | 0.074 <sup>a</sup>    |
| Creatine (mg/dL)             | 3.684 [0.40-8.73]     | 0.011          | -0.082                             | 0.497 <sup>b</sup>    |
| PPT (seconds)                | 18.144 ± 16.838       | 0.63           | -0.184                             | 0.124 <sup>a</sup>    |
| APTT (seconds)               | 32.754 ± 12.807       | 0.58           | -0.076                             | 0.530 <sup>a</sup>    |
| NYHA Classifications         |                       |                |                                    |                       |
| I                            | 10 (13.9%)            |                |                                    |                       |
| II                           | 9 (12.5%)             |                |                                    |                       |
| III                          | 47 (65.3%)            |                |                                    |                       |
| IV                           | 6 (8.3%)              |                |                                    |                       |

\*The normality analysis was performed using the Kolmogorov-Smirnov test, with a significance level set at  $p < 0.05$ . \*The correlation analysis was performed using: <sup>a</sup> Pearson Correlation Test; and <sup>b</sup> Spearman Rho Test. The results were considered significant if  $p < 0.05$ . Results lacking homogeneity are presented with median and IQR. HF: heart failure; SGOT: serum glutamic oxaloacetic transaminase; NYHA: New York Heart Association; SGPT: serum glutamic pyruvic transaminase; APTT: activated partial thromboplastin time; PTT: partial thromboplastin time; PCT: procalcitonin.

**Table 2 – Results of analysis of mean differences of PCT and D-dimer on HF stages.**

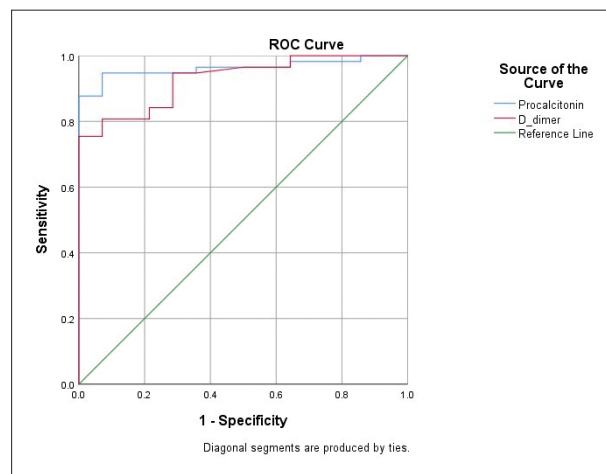
| Variables | NYHA HF Classifications |               |               |                 | p-value              |
|-----------|-------------------------|---------------|---------------|-----------------|----------------------|
|           | I                       | II            | III           | IV              |                      |
| PCT       | 0.533 ± 0.096           | 2.255 ± 1.923 | 3.691 ± 2.646 | 63.752 ± 61.274 | < 0.001 <sup>*</sup> |
| D-dimer   | 1.245 ± 0.342           | 1.845 ± 1.254 | 4.497 ± 3.515 | 22.853 ± 14.446 | < 0.001 <sup>*</sup> |

\*The analysis was performed using the ANOVA test, with a significance level set at  $p < 0.05$ . NYHA: New York Heart Association; PCT: procalcitonin; HF: heart failure.

**Table 3 – Post-hoc analysis of mean differences in PCT across HF stages**

| NYHA HF Classifications | PCT      | D-Dimer |
|-------------------------|----------|---------|
|                         | P-value  | P-value |
| I vs II                 | 0.343    | 0.886   |
| I vs III                | < 0.001* | 0.002*  |
| I vs IV                 | 0.01*    | 0.038*  |
| II vs III               | 0.282    | 0.037*  |
| II vs IV                | 0.01*    | 0.067   |
| III vs IV               | < 0.001* | 0.005*  |

\*The analysis was performed using the Mann-Whitney test with Bonferroni correction, with a significance level set at  $p < 0.0083$ . NYHA: New York Heart Association; PCT: procalcitonin.



**Figure 1 – ROC curves of PCT and D-dimer on HF stages. ROC: receiver operating characteristic.**

PCT synthesis is markedly upregulated in various tissues, including the liver, lungs, and kidneys.<sup>18</sup> This upregulation is driven by pro-inflammatory cytokines, such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-1 beta (IL-1 $\beta$ ), and interleukin-6 (IL-6), as well as bacterial endotoxins.<sup>19</sup> In the context of CHF, elevated PCT levels may be indicative of a heightened inflammatory state, which is increasingly recognized as a key driver of disease progression in HF. The inflammatory milieu in CHF can lead to systemic effects that exacerbate cardiac dysfunction, including endothelial dysfunction, increased vascular permeability, and adverse cardiac remodeling.<sup>10</sup> As such, elevated PCT levels may reflect a state of systemic inflammation and immune activation, both of which are associated with worse clinical outcomes and greater disease severity in CHF patients. Even so, studies investigating the value of PCT testing in various CHF stages are still minimal. Thus, this study aims to evaluate the efficacy of

**Table 4 – AUC for PCT and D-dimer**

| Variable | Cut-off values | AUC   | Standard Error | p        | 95% CI        |
|----------|----------------|-------|----------------|----------|---------------|
| PCT      | 1.190          | 0.962 | 0.021          | < 0.001* | 0.921 - 1.000 |
| D-Dimer  | 2.110          | 0.929 | 0.031          | < 0.001* | 0.868 - 0.989 |

\*The analysis was conducted using ROC analysis. Results were considered significant if  $p < 0.05$ . AUC: area under the curve; CI: confidence interval; PCT: procalcitonin.

**Table 5 – Multivariate analysis of HF stages**

| Variables | B     | Standard Error | P-value  | 95% CI        |
|-----------|-------|----------------|----------|---------------|
| Constants | 2.015 | 0.457          |          |               |
| D-Dimer   | 0.067 | 0.017          | < 0.001* | 0.034 – 0.101 |
| PCT       | 0.004 | 0.007          | 0.561    | 0.009 – 0.017 |

\*The analysis was performed using the Linear Regression Test. Results were considered significant if  $p < 0.05$ . CI: confidence interval; PCT: procalcitonin.

PCT levels as a prognostic marker for predicting outcomes in various CHF stages. Under normal conditions, serum levels of PCT are typically less than 0.05 ng/mL. However, this value can multiply by 100 or 1000 due to the presence of endotoxins or cytokines in the body.<sup>20</sup> A study by Boulogne et al. has shown that HF patients had the highest levels of markers for mechanical stress and inflammation. Interestingly, although markers of mechanical stress decreased along with clinical improvement, markers for inflammation stayed at a high level for up to one month subsequent to decompensation.<sup>21</sup> An explanation for this was provided by Anker et al., who stated that the cause for the increase in PCT levels may be due to mesenteric congestion, which leads to the translocation of bacteria from the intestinal lumen into the blood, causing endotoxemia. This explanation was supported by another study by Möckel et al., which suggests that PCT is a marker for immune activation in endotoxemia.<sup>17</sup>

This study found that patients with PCT levels higher than 1.190 ng/mL exhibited greater disease severity compared to patients with lower PCT levels. Specifically, between stages I and III ( $p < 0.001$ ), stages I and IV ( $p < 0.01$ ), stages II and IV ( $p < 0.01$ ), as well as stages III and IV ( $p < 0.001$ ). These results suggest that, while PCT levels differ significantly between patients with risk factors of HF and patients with severe HF (stage III/IV), PCT levels also vary significantly between patients with symptomatic HF (stage III) and patients with advanced HF (stage IV).

The findings of this study corroborate with several other studies, which showed that PCT has both high sensitivity and specificity in the diagnosis and prediction of severity in CHF patients. Canbay et al. found that PCT had a positive predictive

value of 80% [95% CI, 67.6-92.4%] and 85% [73.9-96.1%], respectively, for the diagnosis of HF and decompensated HF, as well as the HF stage, in both inpatients and outpatients.<sup>12,22</sup> Loncar et al. discovered similar data on the relationship between elevated PCT and mortality, and Cox regression analysis revealed that baseline PCT had a significant predictive value for hospitalization or all-cause death on day 90 (AUC: 0.67;  $p = 0.013$ ). The worst outcome was observed in patients with persistently rising or increased PCT levels within the first 72 hours of admission ( $p = 0.0002$ ).<sup>23</sup> Another study by Li et al. has shown that PCT levels are associated with decreased exposure to antibiotics, shorter duration of stay, and decreased cost.<sup>24</sup> PCT is also a reliable marker of HF with reduced ejection fraction (HFrEF), showing a significant correlation with a 24-month mortality rate.<sup>11</sup> A study on the prognostic performance of various cardiovascular biomarkers found that there is an independent correlation between increasing PCT levels and a decrease in event-free survival among HF individuals.<sup>25</sup> As per the previous studies mentioned, individuals with acute heart failure (AHF) who presented PCT levels  $> 0.08$  ng/mL on day 120 were associated with a greater likelihood of mortality from a variety of reasons compared to those who had PCT levels  $\leq 0.08$  ng/mL (log-rank  $p = 0.0123$ ), according to research by Darche et al. It is worth mentioning that individuals with acute infections were not included in the research.<sup>26</sup>

In contrast, these findings contradict a review conducted by the Biomarker Study Group of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC), which deems PCT as an unreliable independent biomarker in diagnosing AHF.<sup>27</sup> A randomized study conducted across 16 sites in Europe, titled the IMPACT-EU trial, investigated the effect of testing for PCT levels on antibiotic therapy in improving clinical outcomes. As opposed to their hypothesis, PCT-guided antibiotic therapy proved to show no benefits compared to standard antibiotic therapy in HF patients.<sup>25</sup> This suggests that, apart from the benefits of using PCT levels as a prognostic marker, it shows no significant impact on HF patients with concomitant bacterial infection.

## D-dimer

D-dimer is a fibrin degradation product that is formed during the breakdown of cross-linked fibrin, a key component of blood clots. Elevated D-dimer levels are indicative of increased fibrinolytic activity. They are often seen in conditions associated with heightened thrombotic and fibrinolytic states, such as venous thromboembolism, disseminated intravascular coagulation (DIC), and severe infections.<sup>28</sup> In the context of CHF, elevated D-dimer levels may reflect a pro-thrombotic state that is driven by a combination of factors, including endothelial dysfunction, systemic inflammation, and venous stasis.<sup>29-31</sup> CHF is associated with increased activation of the coagulation cascade, leading to the formation of microthrombi within the microcirculation.<sup>32</sup> These microthrombi can exacerbate cardiac dysfunction by impairing coronary blood flow and contributing to myocardial ischemia.<sup>33</sup> Furthermore, the presence of microthrombi can lead to the release of additional pro-inflammatory cytokines, further amplifying the inflammatory response and contributing to adverse outcomes

in CHF.<sup>34</sup> Therefore, elevated D-dimer levels in CHF patients may serve as a marker of both the underlying pro-thrombotic state and the associated systemic inflammation, both of which are linked to increased disease severity and worse prognosis.

Multiple studies have pointed to an increased all-cause mortality in populations with elevated D-dimer levels. Yet, the role of D-dimer in predicting the outcomes or prognosis in HF patients remains unclear.<sup>9</sup> Thus, this study explored the associations of increased D-dimer levels with the severity of HF and found that the optimal cutoff is 2.110 ng/mL through a ROC analysis. Similar to the mean differences of PCT, the mean differences of D-dimer are found to be significantly correlated between stages I and III ( $p = 0.002$ ), stages I and IV ( $p = 0.038$ ), stages II and III ( $p = 0.037$ ), as well as stages III and IV ( $p = 0.005$ ). These results show that D-dimer may be a more promising candidate as a marker of severity compared to PCT. This is further validated through multivariate analysis, with D-dimer showing a significant correlation with the HF stages.

The results of the study align with the results of a study by Tan et al., showing that HF patients with high levels of D-dimer had a higher mortality risk by more than twofold (HR 2.34; 95% CI 1.33 to 4.13). The possible explanation for this was that individuals with HF are more prone to blood clotting abnormalities and present a higher likelihood of experiencing thromboembolic incidents. This may be linked to inflammation, neurohormonal activation, and endothelial dysfunction, which may trigger fibrinolytic activity and, consequently, increase the levels of D-dimer.<sup>25</sup> Several findings were made by Moss et al., who discovered that recurrent cardiac events were linked to high D-dimer levels two months after an acute myocardial infarction.<sup>35</sup> Research by Akgul et al. discovered that D-dimer had a comparable predictive impact on troponin-T in the prognosis of STEMI patients, with a sensitivity of 70.6% and specificity of 79.2%, in addition to prognosis for recurrence and death.<sup>36</sup> Therefore, D-dimer levels have the potential to forecast the course of the disease and assess mortality in individuals with HF.

Prothrombotic and hemostatic disorders are linked to HF. All three elements of Virchow's triad — stasis, endothelial damage, and hypercoagulability — undergo various modifications in HF patients despite the fact that the precise processes generating hemostatic abnormalities in HF are not yet fully understood.<sup>37</sup> The optimal D-dimer cut-off value was found to be 0.84 mg/L in a study by Huang et al.. It was independently linked to an increased risk of long-term mortality (HR = 2.315, 95% CI: 1.570-3.414,  $p < 0.001$ ) and major adverse cardiovascular events (MACE) (HR = 1.256, 95% CI: 1.058-1.490,  $p = 0.009$ ), unaffected by age or gender.<sup>14</sup> Bittencourt et al. discovered that the D-dimer cut-off value for predicting in-hospital death was 1.433 mg/dL ( $p = 0.03$ ), with a sensitivity of 80% and specificity of 69% in 70 decompensated HF patients (85.7% with NYHA class IV). Additionally, it was shown that patients with D-dimer levels  $> 2.000$  mg/dL had the poorest prognosis, with an event-free survival of just 70 days, as opposed to those with D-dimer levels  $\leq 2000$  mg/dL, who had an event-free survival of 295 days ( $p = 0.03$ ).<sup>38</sup> After a one-year follow-up, Huang et al. discovered that, in the research sample, high D-dimer levels (D-dimer level  $> 0.56$  g/mL FEU) independently predicted all-cause death in HFrEF (HR: 1.49;  $p = 0.039$ ) and HFpEF (HR:

2.06;  $p = 0.033$ ).<sup>39</sup> In-hospital mortality was independently related to a high D-dimer level ( $> 3.85$  g/mL) upon hospital admission, according to the research by Minami et al. (adjusted OR: 11.48; CI 95%: 2.54-51.85;  $p = 0.002$ ).<sup>40</sup> It is worth noting that a study by Zhang et al. reported that the D-dimer levels of HF patients were found to be higher in women than in men. This implies that the ideal D-dimer cut-off values could vary between genders, which may pose a challenge when it comes to using the D-dimer levels as a prognostic tool. Nevertheless, the study also found that the D-dimer levels are significantly correlated with the incident of HF in both men and women.<sup>9</sup>

The associations between PCT and D-dimer levels and CHF severity may be confounded by factors such as the patient's age, comorbidities, and infections, particularly in the context of the COVID-19 pandemic. Older patients and those with conditions such as chronic kidney disease or diabetes may exhibit elevated baseline biomarker levels, independent of HF severity. Additionally, viral infections can further elevate these biomarkers, affecting how their prognostic value are interpreted. To address these confounders, stratified analyses based on age, comorbidities, and infection status are essential. Moreover, variability in laboratory methods for measuring PCT and D-dimer levels adds another layer of complexity. Standardizing these assays is crucial for establishing reliable cut-off values and ensuring consistent results across studies. Although efforts were made in this study to maintain measurement consistency, discrepancies in laboratory methodologies could limit the generalizability of the findings. A robust multivariate analysis, incorporating variables such as ejection fraction, renal function, and inflammatory markers, is vital to assess the independent prognostic value of PCT and D-dimer accurately. In this study, D-dimer was significantly correlated with CHF severity after adjusting for other variables, underscoring its potential as a prognostic marker. At the same time, the non-significant results for PCT suggest a more context-dependent role, which requires further research. This study was conducted with a limited sample size in a single center and, therefore, must be carefully extrapolated when applied to populations with different ethnic backgrounds. This study was also carried out in the middle of the COVID-19 pandemic and may result in higher PCT and D-dimer levels in patients with undetected concomitant infection. Given the observational nature of this study, there may be uncontrollable confounding factors affecting the results.

## Conclusions

In conclusion, CHF remains a complex and clinically significant syndrome associated with substantial morbidity and mortality. The variables of PCT and D-dimer levels

were shown to be significantly correlated with the HF stages in this study. Significant mean differences in PCT and D-dimer levels in various stages were discovered. Multivariate analysis revealed a strong correlation between D-dimer and the HF stages, indicating its potential as a paramount severity marker in HF patients compared to PCT. It offers potential clinical implications in risk stratification and management strategies for CHF patients. Further research in larger cohorts is warranted to validate these findings and explore the full clinical benefits of D-dimer in CHF.

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## Author Contributions

Conception and design of the research: Liyis BG; acquisition of data: Liyis BG, Sutedja JC, Mareska V, Salim A; analysis and interpretation of the data and statistical analysis: Sadeva IGKA; writing of the manuscript: Liyis BG, Sutedja JC, Mareska V, David G, Gunawan MFB, Nathaniel J; critical revision of the manuscript for intellectual content: David G, Gunawan MFB, Nathaniel J, Wihandani DM, Sutanegara BAPD.

## Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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This study is not associated with any thesis or dissertation work.

## Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee on Animal Experiments of the Research Ethics Committee Faculty of Medicine Universitas Udayana under the protocol number 972/UN14.2.2.VII/14/LT/2022.

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