(International Print/Online Journal)

SJIF IMPACT FACTOR: 5.565
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume 5, Issue 3, Page No: 206-213
May-June 2022

IJMSCR

# Study of Serum Ferritin And Its Correlation With Serum Pro BNP (Brain Natriuretic Peptide) Levels In Heart Failure Patients

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Type of Publication: Original Research Paper
Conflicts of Interest: Nil

**Abstract:**

Brain natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) are known as diagnostic and prognostic markers in Heart failure (HF). Iron deficiency (ID) is a common co-morbidity that often coexist in patients with HF which can be diagnosed by estimating serum ferritin. The present study evaluates the correlation between Serum Ferritin and Serum proBNP levels in patients with HF.

**Materials And Methods:**

A total of 99 patients with HF, aged >18 years of either gender and with proBNP level ≥900pg/ml were included in the study. HF was classified as per New York Heart Association (NYHA). The following parameters were evaluated; Age (years), Systolic Blood Pressure (mmHg), Diastolic Blood Pressure (mmHg), WBC ($10^3$/cumm), Haemoglobin(g%), Serum Ferritin (ng/ml), Serum Potassium (mmol/L) (IU/L), SGPT (IU/L), Serum Cholesterol(mg/dL), Serum Triglyceride(mg/dL), Serum Urea (mg/dl), Serum Creatinine (mg/dl), Serum Sodium (mmol/L), Serum Potassium (mmol/L), and Serum proBNP (pg/ml). The Serum ferritin was correlated with above parameters and also with NYHA classification.

**Results:**

The results were statistically significant between serum proBNP and serum ferritin level both for the values 100 ng/ml (p=0.00005). The functional classification of Heart failure (NYHA) was also significantly associated with Serum Ferritin levels with a p-value of 0.04952.

**Conclusion:**

In patients with Heart failure, serum ferritin could be a reliable predictor of unfavourable outcome, depending on the grades and severity of heart disease. Serum Ferritin and BNP levels may potentially represent a beneficial addition to the standard medical management of Heart Failure.

**Keywords:** Nil

## Introduction:

Heart failure (HF) is a clinical syndrome resulting in impairment of ventricular filling or the ejection of blood to the systemic circulation caused by functional and structural defects in myocardium [1]. An estimated global burden of 116 million deaths has been attributed to HF as one of its causes [2]. Around 5.7 million people in the United States of America (USA) have HF. These projections seem worrisome as the cases of HF may rise to more than 8 million people by 2030, accounting for a 46 % increase in prevalence [3]. In India, HF cases range between 1.3 and 4.6 million, which sums up to a prevalence of

0.12–0.44 %, although this can be underestimated [4].

The common aetiologies of HF are increased hemodynamic overload, ventricular remodelling, abnormal myocyte calcium cycling, ischemia-related dysfunction, excessive or inadequate proliferation of the extracellular matrix, excessive neuro-humoral stimulation, accelerated apoptosis and genetic mutations [5]. Though the underlying pathogenesis of HF is unclear yet, the proposed theory includes excessive neuro-endocrine activation and the release of pro- inflammatory cytokines following a cardiac insult. This leads to the release of endotoxins, nitric oxide, adhesion molecules, and reactive oxygen species, which worsens HF [6].

Brain natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) have clinical significance both as diagnostic and prognostic markers in the management of HF [7]. Responses like pressure overload and volume expansion trigger the increased secretion of BNP and proBNP by the cardiomyocytes [8,9].

Iron deficiency (ID) is a common co-morbidity that often coexist in patients with HF. Hemoglobin <13g/dl in men and <12g/dl in women is clearly defined as anaemia in patients with HF [10]. The association between mortality in HF and hemoglobin level is non-linear, and low Hemoglobin increases the risk [11]. Studies demonstrated ID as a strong, independent

predictor of unfavourable outcomes in chronic heart failure [12]. Hemoglobin and serum ferritin can be utilized for the definitive diagnosis of ID [13]. Further, studies demonstrated the favourable outcome of intravenous iron therapy in patients with HF [14]. Therefore, the present study was conducted to evaluate the correlation between Serum Ferritin and Serum proBNP levels in patients with HF.

**Material & Method:**

This was a single centre, hospital-based, observational cross-sectional study conducted in the Department of Medicine, Pt.J.N.M. Medical College and Dr. Bhim Rao Ambedkar Memorial Hospital, RAIPUR, CG, over two years from September 2019 to August 2021. The calculated sample size was 99. The study was approved by the Institutional Ethics Committee, and written informed consent was obtained from the participants.

Patients with heart failure, aged >18 years of either gender and with proBNP level ≥900pg/ml were included in the study. Patients with major systemic disease or co-morbidities or who have received iron supplements/blood transfusion in the previous four weeks, or lactating/ nursing mothers were excluded from the study. Heart failure was diagnosed on the basis of clinical examination, biochemical analysis, electrocardiography and echocardiographic findings. Heart failure was also classified as functionally suggested by the New York Heart Association (NYHA) [15].

The following demographic and clinical parameters were evaluated in the study; Age (years), Systolic Blood Pressure (mmHg), Diastolic Blood Pressure (mmHg), WBC ($10^3$/cumm), Haemoglobin(g%), Serum Ferritin (ng/ml), Serum Potassium (mmol/L) (IU/L), SGPT (IU/L), Serum Cholesterol(mg/dL), Serum Triglyceride(mg/dL), Serum Urea (mg/dl), Serum Creatinine (mg/dl), Serum Sodium (mmol/L), Serum Potassium (mmol/L), and Serum proBNP (pg/ml). The Serum ferritin was correlated with above parameters described. The serum ferritin was also compared with Functional classification of Heart failure (New York Heart Association)

Descriptive data like mean, SD etc., were calculated from quantitative parameters. Frequency distributions were presented tabular and graphically for checking the normality of data. Pearson's correlations were used to check the association between proBNP with different

quantitative parameters. Also, we used chi-square test for association between categorical variables, i.e. functional classification with level of Serum Ferritin. The student's t-test was used to test significance. p-value < 0.05 was considered significant. All statistical analyses were performed in Microsoft Excel and SPSS 22.0.

**Results:**

A total of 99 patients with heart failure with proBNP levels≥ 900pg/ml were enrolled in the study. The minimum, maximum, median and mean with



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standard deviation values of various demographic and clinical parameters are detailed in Table:1.

The serum ferritin level was statistically correlated with the above parameters. The results were statistically significant between serum proBNP and serum ferritin level both for the values

<100 ng/ml (p=0.000175) and >100 ng/ml (p=0.00005). However, insignificant results were obtained for other variables. The scatter plot between Serum proBNP and Serum Ferritin (<100 ng/ml), and Serum Ferritin (>100 ng/ml) is shown in Figures 1 & 2.

The functional classification of Heart failure (New York Heart Association; NYHA) was significantly associated with Serum Ferritin levels with a p-value of 0.04952. The detailed findings are elicited in Table:2.

**Discussion:**

In the diagnosis of Heart failure, NT-proBNP has the advantages of being economical, simple and reproducible in clinical detections. The N-terminal pro-brain natriuretic peptide is secreted and produced by the heart when pressure and volume loads increase in the atria and ventricles. Iron deficiency is a common co-morbidity present in approximately half of the patients with HF, which may have multifaceted clinical after-effects. It causes impaired erythropoiesis and marked impairment of oxidative metabolism, cellular energetics, and immune mechanisms. Iron deficiency with and without anaemia is accompanied by reduced exercise capacity, impaired quality of life and poor prognosis and its correction improves cognitive, symptomatic, and exercise performance. Until recently, there has been little known data about Heart failure and its relation with Ferritin and proBNP. Therefore, we evaluated Serum Ferritin and its correlation with Serum proBNP levels in Heart failure patients.

In current study, the correlation between serum proBNP and serum ferritin level was statistically significant for both values of <100 ng/ml (p=0.000175) and >100 ng/ml (p=0.00005). The functional classification of heart failure (New York Heart Association) correlated significantly with serum ferritin levels (p-0.04952). But no statistically significant association was established between proBNP and other variables described.

In our study, the mean age of patients with iron deficiency and heart failure was 56.27±12.55 years, with majority falling in the age group 50 to 60 years (31.3%). Male preponderance was seen in this study (63.6% vs 36.4%) with a male: female ratio of 1.75:1. The findings of our study were in concordance with Anker et al.[16], Jankowska et al.[12] and Xu et al.[17].

In the current study, the mean SBP of patients was 108.1±14.7 mmHg and mean DBP was 68.84±10.53 mmHg, with majority having SBP in the range of 90 to 100 mmHg (30.3%) and DBP in the range of 60 to 70 mmHg (37.4%). Similar results were also demonstrated by Toblli

et al., supporting our findings[18]. On the contrary, higher systolic and diastolic blood pressure levels were evident in the study, where the mean systolic and diastolic pressure found was

134.3 ± 29.9 and 76.8 ± 18.9 mmHg [19]. Similarly, Lee et al. also found a higher range of systolic and diastolic pressure of 131 +30.3 and 78 + 18.8 mmHg, respectively, in his study [20].

We found mean Haemoglobin level as 11.99 ± 1.91 g%, with majority of patients in the range of 10 to 12 g% (45.5%). This was contrary to Jankowska et al., where the mean Haemoglobin level was 13.6 + 1.6 g% in patients with Heart failure and iron deficiency [12]. Patients with HF are prone to become iron deficient as a consequence of depletion of iron stores (absolute ID) or more frequently as a result of impaired iron metabolism in the course of inflammatory processes characterizing CHF (functional ID) [21]. In HF, pro-inflammatory cytokines activate that block the intestinal absorption of iron and divert iron from the circulation into the reticuloendothelial system, causing reticuloendothelial block [22]. However, it is worth mentioning that, although Hb levels may be low in some patients with HF, this can be due to a dilution factor and may not necessarily be due to iron deficiency per se [18].

The mean Serum Ferritin level in the present study was 50.7±47.79 ng/ml. Maximum patients had Serum Ferritin in 0 to 20 ng/ml (49.5%). The mean Serum Ferritin levels matched our findings in a study done by Anker et al. [12]. In the current study, mean SGOT, SGPT levels found were 69.7± 78.2 and



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55.87±107.52 IU/L, respectively. In a study by Allen et al., liver function test abnormalities were common in patients with HF with highly elevated SGOT and SGPT levels, contrary to our study findings where levels are were not very highly raised [23].

Although the serum cholesterol, triglyceride and renal function parameters (serum urea, creatinine, sodium, potassium were within the normal range in the majority of the patients. Chronic hypoxia due to anaemia may induce overexpression of pro-inflammatory cytokines

(tumour necrosis factor-α and interleukin-6), which are partially responsible for perpetuating the inflammatory status in patients with CHF and renal dysfunction as well as potentiating the relative iron deficiency by stimulating hepcidin [24].

We found the mean proBNP level was 1043.2± 287.9 pg/ml. Serum proBNP of 900pg/ml was prevalent in maximum cases (22.2%), and 15.2% of cases had extensively raised more than 1025 pg/ml. Similarly, Jankowska et al. found pro-BNP levels above 900 in patients with Heart failure with Iron deficiency anaemia. They supported our study finding of higher plasma proBNP and a borderline trend towards the more advanced NYHA class in these patients [12]. One of the most useful tests for evaluating the status of patients with HF is proBNP, not only for systolic but also for diastolic LV dysfunction [25]. A single measurement of proBNP in patients with advanced HF can help identify patients at a higher risk of death and an even better prognostic marker than anaemia [26].

The limitation of our study was the small sample size and single centre evaluation. Transferrin saturation can be considered for better correlation with proBNP since S. Ferritin can be raised in various other inflammatory conditions which cannot be determined clinically.

**Conclusion:**

In our patients with Heart failure, Serum Ferritin was a reliable predictor of an unfavourable outcome, depending on the grades and severity of heart disease. Serum proBNP levels and Serum Ferritin levels were correlated to each other. Similarly, NYHA grades were statistically significantly associated with Serum Ferritin levels in our study. These findings suggest that Serum Ferritin and BNP levels may potentially represent a beneficial addition to the standard medical management of Heart Failure. Further studies will aid in explaining the pathophysiology of deranged Ferritin stores seen in the course of Heart Failure linked to detrimental effects of iron deficiency in Heart failure correlating with Pro-BNP levels.

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**Tables And Figures:**

**Table 1: Descriptive statistics of demographic and clinical parameters**

| Parameters | Minimum | Maximum | Median | Mean ± SD |
|---|---|---|---|---|
| Age (years) | 22 | 88 | 58 | 56.27 ± 12.55 |
| Systolic Blood Pressure (mmHg) | 80 | 180 | 110 | 108.1 ± 14.7 |
| Diastolic Blood Pressure (mmHg) | 50 | 110 | 70 | 68.84 ± 10.53 |
| WBC ($10^3$/cumm) | 4 | 12.8 | 8.76 | 8.36 ± 2.4 |
| Haemoglobin (g%) | 10 | 17.2 | 11.2 | 11.99 ± 1.91 |
| Serum Ferritin (ng/ml) | 3 | 160 | 29 | 50.7 ± 47.79 |
| SGOT (IU/L) | 13 | 500 | 49 | 69.7 ± 78.2 |
| SGPT (IU/L) | 10 | 960 | 33 | 55.87 ± 107.52 |
| Serum Cholesterol (mg/dL) | 88 | 300 | 167 | 170.5 ± 47.1 |
| Serum Triglyceride (mg/dL) | 57 | 424 | 120 | 145.8 ± 70.1 |
| Serum Urea (mg/dl) | 11 | 43 | 22 | 24.83 ± 9.19 |
| Serum Creatinine (mg/dl) | 0.3 | 1.7 | 0.8 | 0.84 ± 0.31 |
| Serum Sodium (mmol/L) | 13 0 | 145 | 137 | 137.23 ± 2.16 |
| Serum Potassium (mmol/L) | 3.1 | 4.5 | 3.7 | 3.72 ± 0.25 |
| Serum proBNP (pg/ml) | 900 | 2090 | 966 | 1043.2 ± 287.9 |



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**Table 2: Association between Serum Ferritin level and Functional classification of Heart failure (New York Heart Association; NYHA)**

| | Functional classification | Serum Ferritin | | Chi-square test | P -value | Significance |
|---|---|---|---|---|---|---|
| | | ≤ 100 | > 100 | | | |
| Serum ferritin | NYHA 1 | 17 | 10 | 7.836 | 0.04952 | **Significant** |
| | NYHA 2 | 38 | 8 | | | |
| | NYHA 3 | 16 | 1 | | | |
| | NYHA 4 | 8 | 1 | | | |

**Figure 1: Scatter plot between serum proBNP and serum ferritin (<100 ng/ml)**

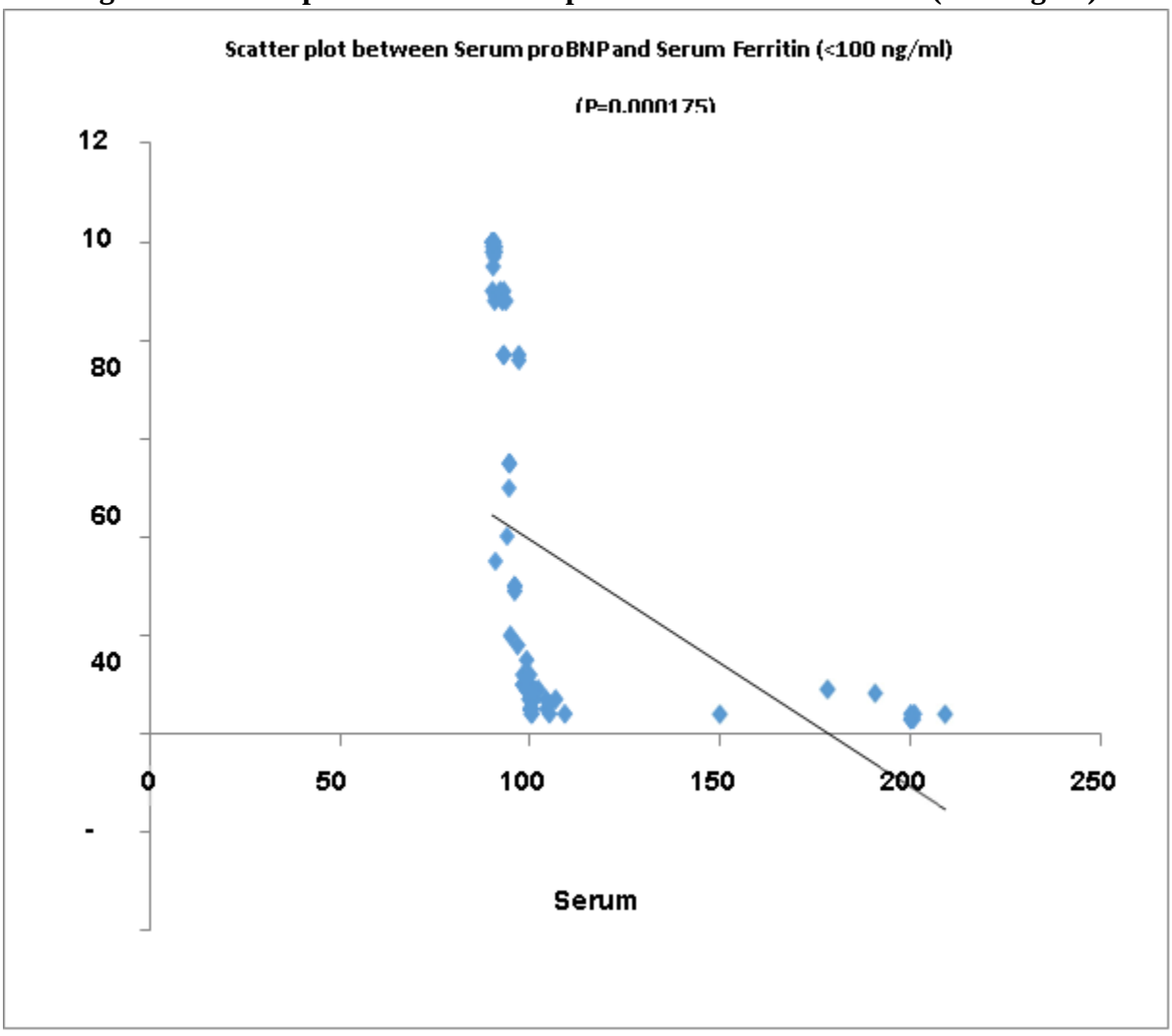




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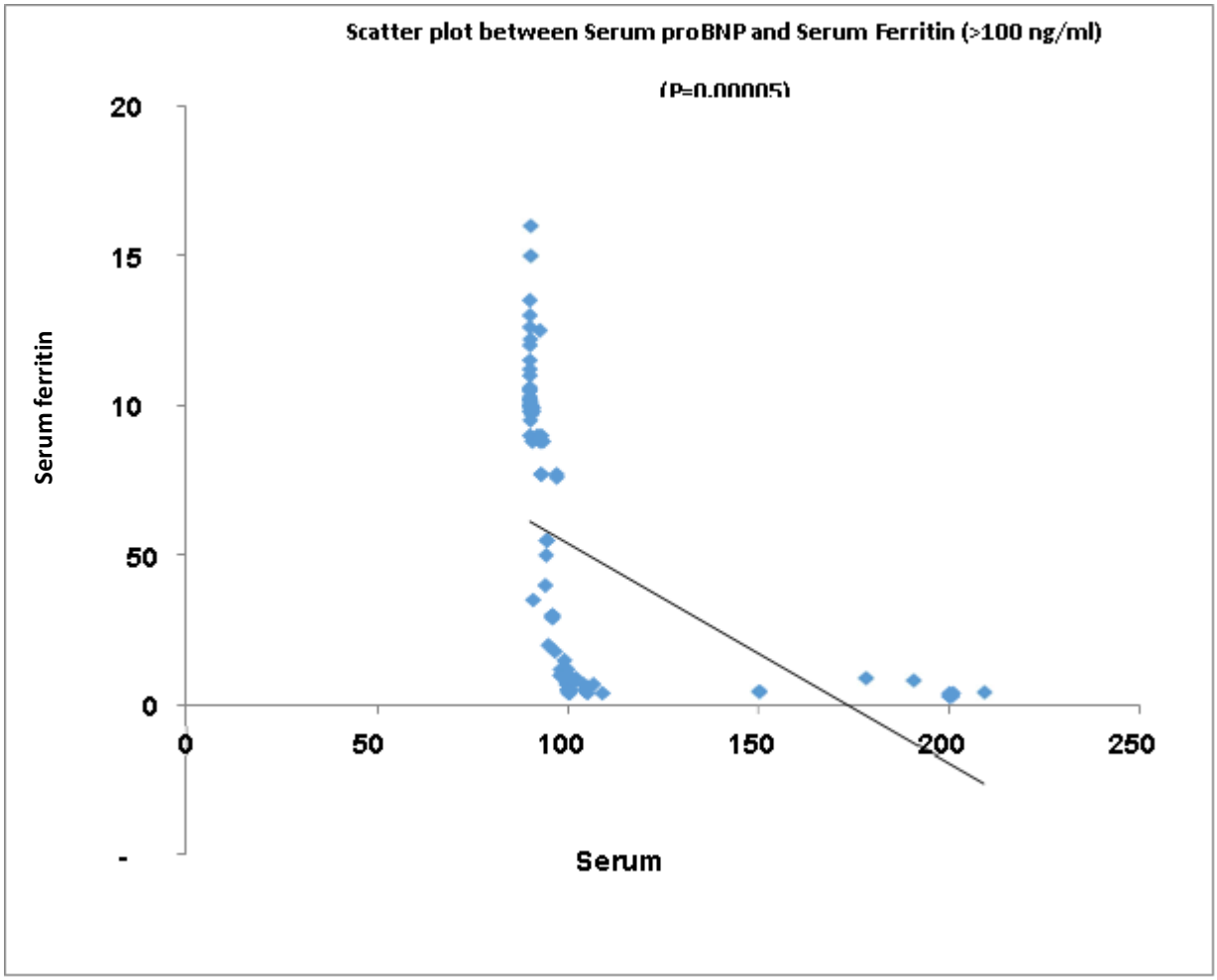
**Figure 2: Scatter plot between serum proBNP and serum ferritin (>100 ng/ml)**



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