ORIGINAL RESEARCH

A cross-sectional observational study of serum parathyroid hormone levels and its relation with severity and duration of heart failure

[1]Sukhjiwan Singh Bhandal, [2]Arshdeep Saggi, [3]Navjiwan Singh Bhandal

Corresponding author
Arshdeep Saggi
Email: saggiarshdeep@gmail.com

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ABSTRACT

Aim: A cross-sectional observational study of serum parathyroid hormone levels and its relation with severity and duration of heart failure. **Material and methods:** The present study included a cohort of 80 consecutive outpatients diagnosed with systolic heart failure. The echocardiogram revealed that the left ventricular ejection fraction (LVEF) was less than 40% in all of the patients. Blood samples were obtained in order to measure intact parathyroid hormone (PTH) and brain natriuretic peptide (BNP). Serum intact parathyroid hormone (PTH) levels were collected at an outpatient clinic utilizing an Immulite intact PTH assay manufactured by Diagnostics Product Corporation in 2000, located in Los Angeles, California. The assay's established normal range was determined to be between 10 and 65 pg/ml. The patients were categorized into four distinct groups according to the New York Heart Association (NYHA) functional class. **Results:** The mean left ventricular ejection fraction (LVEF) was found to be 26.85±7.78, while the mean parathyroid hormone (PTH) level was measured to be 102.55±13.55 pg/ml. Sixteen patients (20%) exhibited advanced heart failure, as determined by the New York Heart Association functional class IV. The study observed a significant association between serum intact parathyroid hormone (PTH) levels and various clinical parameters in patients diagnosed with heart failure (HF). These parameters included B-type natriuretic peptide (BNP) levels, left ventricular ejection fraction (LVEF), heart rate, creatinine clearance, left atrial size, left ventricular diastolic diameter, diuretic usage, presence of atrial fibrillation, and hemoglobin levels. Based on the analysis of the receiver operator characteristic curve, it was determined that a PTH cut-off value of >95.85 pg/ml is optimal for predicting advanced HF. This cut-off value yielded a sensitivity of 94.15% and a specificity of 65.24%. **Conclusion:** we concluded that the serum parathyroid hormone (PTH) levels has the potential to offer additional valuable insights and serve as a straightforward biomarker approach for classifying individuals with advanced heart failure (HF) who exhibit elevated PTH levels.

Keywords: Parathyroid hormone, Heart failure, LVEF, NYHA

INTRODUCTION

Heart failure is a significant public health issue on a global scale, characterized by substantial rates of illness and death. According to data obtained from NHANES 2009 to 2012, it is estimated that approximately 5.7 million individuals in the United States are affected by heart failure. Furthermore, projections indicate that this number will increase to over 8 million patients by the year 2030.[2,3] Heart failure is a prevalent medical condition that impacts a substantial number of individuals, estimated to be around 4 million. In China alone, there are approximately 550,000 newly diagnosed cases of heart failure reported each year.[4] There are numerous potential risk factors that contribute to the onset of heart failure. The alteration of these risk factors has the potential to mitigate the occurrence of heart failure and lower the mortality rate among individuals already diagnosed with heart failure. Hence, it is imperative to promptly identify these modifiable risk factors. The secretion of parathyroid hormone (PTH) is facilitated by the parathyroid glands, which are responsible for regulating calcium homeostasis. The excessive presence of parathyroid hormone (PTH) may have negative implications on cardiovascular well-being that extend beyond its role in regulating calcium and phosphate levels within the body.[5] Numerous observational studies have been conducted thus far to investigate the correlation between the circulating level of parathyroid hormone (PTH) and the subsequent risk of heart failure in the general population [7-9], as well as the adverse

outcomes in patients diagnosed with heart failure.Nevertheless, this correlation was not detected in all of the conducted studies. The presence of contradictory findings in the various studies can be partially attributed to variations in the study population, lack of standardization in the measurement of parathyroid hormone (PTH), differences in the duration of follow-up, disparities in gender representation, and inadequate adjustment for confounding factors. A meticulously conducted meta-analysis has demonstrated a positive correlation between elevated levels of parathyroid hormone (PTH) in the bloodstream and an increased susceptibility to cardiovascular events. Furthermore, a recently conducted meta-analysis specifically examined the correlation between elevated levels of parathyroid hormone (PTH) in the bloodstream and the risk of cardiovascular disease or mortality from any cause.[10]

MATERIAL AND METHODS

The present study included a cohort of 80 consecutive outpatients diagnosed with systolic heart failure. The echocardiogram revealed that the left ventricular ejection fraction (LVEF) was less than 40% in all of the patients. The exclusion criteria for this study included patients who had a creatinine clearance of less than 60%, experienced a recent exacerbation within one month, had a history of long-term alcoholism, were diagnosed with sepsis, pancreatitis, primary hyperparathyroidism, cancer, or severe hepatic disease, or were currently taking spironolactone.

Blood samples were obtained in order to measure intact parathyroid hormone (PTH) and brain natriuretic peptide (BNP). Serum intact parathyroid hormone (PTH) levels were collected at an outpatient clinic utilizing an Immulite intact PTH assay manufactured by Diagnostics Product Corporation in 2000, located in Los Angeles, California. The assay's established normal range was determined to be between 10 and 65 pg/ml.

The patients were categorized into four distinct groups according to the New York Heart Association (NYHA) functional class. In order to classify functional classes, it was necessary to obtain the consensus of two experienced clinicians who were blinded to each other. In the event of a divergence of opinions, a tertiary perspective was sought from a proficient medical practitioner. According to the criteria established by the World Health Organization, anemia is characterized by hemoglobin levels below 13 g/dl in men and below 12 g/dl in women. Hypertension is characterized by blood pressure levels exceeding 140/90 mm Hg on at least two separate occasions during office measurements or while undergoing antihypertensive treatment. Diabetes mellitus was operationally defined as a condition characterized by a fasting blood glucose level equal to or exceeding 126 mg/dl, or the utilization of antidiabetic treatment. Hyperlipidemia is characterized by the presence of elevated levels of serum low-density lipoprotein cholesterol exceeding 160 mg/dl, total cholesterol exceeding 240 mg/dl, triglyceride levels surpassing 200 mg/dl, low levels of high-density lipoprotein cholesterol below 40 mg/dl, or the utilization of lipid-lowering medications. The presence of coronary artery disease was documented based on three criteria: a clinical history of coronary artery disease, abnormal stress test results indicating ischemia, or documented coronary stenosis exceeding 50%. The evaluation encompassed an examination of rhythm, medications, and hemodynamic findings, including heart rate, systolic blood pressure, and diastolic blood pressure.

In accordance with established protocol, it was recommended that all individuals involved in the study undergo transthoracic echocardiography upon admission. The echocardiographic examinations were conducted using the Vivid 7 system, manufactured by GE Healthcare in Wauwatosa, Wisconsin. Probes with frequencies ranging from 2.5 to 5 MHz were utilized in all of the centers involved in the study. The left ventricular ejection fraction (LVEF) was determined using the modified Simpson method. The determination of chamber sizes was based on the most up-to-date guidelines. The estimation of systolic pulmonary artery pressure was derived by utilizing the tricuspid regurgitant velocity profile and applying the modified Bernoulli equation. The transthoracic echocardiographic examinations were digitally recorded and sent to the central facility for evaluation. The evaluations were conducted offline by an experienced sonographer who was unaware of the study protocol. The research study was conducted in adherence to the ethical principles outlined in the Declaration of Helsinki for human subjects research and received approval from the institutional review board.

The parametric data were presented as the mean plus or minus the standard deviation (SD), while the categorical data were expressed as percentages. Statistical procedures were conducted using SPSS 25.0 (SPSS, Inc., Chicago, Illinois). Receiver operator characteristic (ROC) curve analysis was conducted in order to determine the most suitable threshold of parathyroid hormone (PTH) that would maximize both sensitivity and specificity in predicting advanced heart failure (HF). The calculation of areas under the curve served as a means to quantify the accuracy of the tests. In this study, we conducted a comparison of the areas under the curve utilizing the Z test. Group comparisons were conducted using a 1-way analysis of variance for normally distributed data and Kruskal-Wallis tests for data that were not normally distributed. The chi-square test was employed to analyze the categorical variables among different groups. The evaluation of correlation was conducted using either the Pearson correlation test or the Spearman correlation test. Univariate analysis was

employed to quantify the correlation between variables and advanced heart failure (HF). The variables that demonstrated statistical significance in the univariate analysis were included in a multivariate logistic regression model, using the forward stepwise method. This was done to identify the independent predictors of advanced heart failure. A p-value of 0.05 was deemed to be statistically significant.

RESULTS

The mean age of patients in the entire cohort was 65.87±5.74 years, with 70% being men and 30% being women. The mean left ventricular ejection fraction (LVEF) was found to be 26.85±7.78, while the mean parathyroid hormone (PTH) level was measured to be 102.55±13.55 pg/ml. Sixteen patients (20%) exhibited advanced heart failure, as determined by the New York Heart Association functional class IV. Table 1 presents a comparative analysis of the four distinct patient groups suffering from heart failure. Significant differences were observed in relation to the NYHA functional class with respect to various factors, including body mass index, disease duration, parathyroid hormone (PTH) levels, brain natriuretic peptide (BNP) levels, creatinine clearance, hemoglobin levels, diuretic usage, left ventricular ejection fraction (LVEF), left ventricular diastolic diameter, and left atrial size. The study findings indicate a positive correlation between the levels of parathyroid hormone (PTH) and the New York Heart Association (NYHA) functional class, suggesting that as the NYHA functional class increases, there is a corresponding increase in PTH levels.

The study observed a significant association between serum intact parathyroid hormone (PTH) levels and various clinical parameters in patients diagnosed with heart failure (HF). These parameters included B-type natriuretic peptide (BNP) levels, left ventricular ejection fraction (LVEF), heart rate, creatinine clearance, left atrial size, left ventricular diastolic diameter, diuretic usage, presence of atrial fibrillation, and hemoglobin levels (as presented in Table 2).

Table 3 displays the results of univariate logistic regression analyses conducted to identify advanced heart failure (HF). The variables that were identified as indicators of advanced heart failure include the duration of the disease, body mass index, parathyroid hormone (PTH) levels, brain natriuretic peptide (BNP) levels, hemoglobin levels, creatinine clearance, heart rate, systolic blood pressure, left ventricular ejection fraction (LVEF), left ventricular diastolic diameter, left atrial size, presence of atrial fibrillation, and use of diuretics. The results of the multivariate logistic regression analysis indicated a significant association between PTH level and body mass index with advanced HF, as shown in Table 3.

Based on the analysis of the receiver operator characteristic curve, it was determined that a PTH cut-off value of >95.85 pg/ml is optimal for predicting advanced HF. This cut-off value yielded a sensitivity of 94.15% and a specificity of 65.24%.

Table 1 Basic parameter of the patients

	I		**II**		**III**		**IV**		
	(n=18)		**(n=20)**		**(n=26)**		**(n=16)**		
Age (years)	61.25±5.85		68.01±6.64		66.88±3.74		69.74±5.57		0.08
Gender									
Male	14	77.78	12	60	18	69.23	12	75	0.58
Female	4	22.22	8	40	8	30.77	4	25	
Systolic blood pressure (mm Hg)	123.52±4.58		125.22±5.29		119.52±5.74		100.01±6.14		0.04
Diastolic blood pressure (mm Hg)	78.85±3.69		75.44±3.15		75.54±13.33		64.25±3.74		<0.001
Body mass index (kg/m^2)	29.11±3.25		27.15±3.55		27.14±2.52		23.01±3.44		0.001
Heart rate (beats/min)	77.25±8.85		86.85±7.96		89.96±9.88		95.58±8.69		0.04
Left atrial size (mm)	3.99±0.77		4.78±0.88		5.01±0.96		5.33±1.01		<0.001
Atrial fibrillation	1	5.56	6	30	8	30.77	8	50	0.003
Left ventricular ejection fraction (%)	37.02±34.44		28.41±3.64		24.11±4.15		21.98±4.06		<0.001
Left ventricular diastolic diameter (mm)	5.55±0.99		6.01±1.03		6.11±1.11		6.55±1.22		<0.001

Hemoglobin (g/dl)	13.69±1.69		13.01±1.85		13.58±1.69		12.63±1.44		0.02
Systolic pulmonary artery pressure (mm Hg)	36.36±3.85		51.55±5.85		48.85±6.36		45.76±5.94		0.07
Parathyroid hormone (pg/ml)	44.11±5.57		85.49±6.69		120.14±12.52		159.89±13.58		<0.001
Brain natriuretic peptide (pg/ml)	319.89±15.85		1125.19±26.69		1647.15±35.25		2598.66±43.52		<0.001
Creatinine clearance (ml/min)	79.89±3.47		76.48±4.15		78.16±4.12		66.58±2.85		0.002
β Blockers	14	77.78	14	70	17	65.38	10	62.5	0.36
Presence of anemia	5	27.78	6	30	11	42.31	8	50	0.06
Antiplatelet agents	12	66.67	13	65	19	73.08	12	75	0.52
Angiotensin-converting enzyme inhibitor/ angiotensin receptor blocker	14	77.78	14	70	18	69.23	9	65.25	0.22

Table 2 Correlation coefficients for parathyroid hormone

	R	p Value
Left ventricular diastolic diameter	0.37	0.005
Hemoglobin	-0.22	0.033
Left ventricular ejection fraction	—0.52	0.001
Brain natriuretic peptide	0.74	0.001
Creatinine clearance	—0.47	0.001
Heart rate	0.56	0.001
Diuretic usage	0.31	0.001
Left atrial size	0.44	0.001
Atrial fibrillation	0.32	0.002

Table 3 Univariate predictors of advanced heart failure

Hemoglobin	0.77(0.65–1.26)	0.06
Heart rate	1.11(1.21–1.47)	0.002
Brain natriuretic peptide	1.01(1.11–1.52)	0.001
Creatinine clearance	0.88(0.78–0.98)	0.003
Left ventricular ejection fraction	0.99(0.94–1.21)	0.003
Systolic blood pressure	0.96(0.89–1.11)	0.003
Left atrial size	3.54(1.36–5.85)	0.006
Left ventricular diastolic diameter	1.79(1.21–3.58)	0.04
Diuretic usage	4.14(1.17–10.81)	0.03
Atrial fibrillation	3.91(2.01–6.96)	0.007

DISCUSSION

The findings of our study indicate a positive correlation between the severity of NYHA class and the elevation of intact PTH levels in circulation. There was a significant correlation observed between PTH levels and poorer hemodynamic, echocardiographic, and laboratory parameters. Nevertheless, even after accounting for these variables, our analysis revealed a significant correlation between elevated parathyroid hormone (PTH) levels and decreased body mass index (BMI) with the progression of heart failure (HF).

Patients who are decompensated with salt and water retention (NYHA class III and IV HF) exhibit elevated levels of serum aldosterone. In individuals with stable heart failure (classified as NYHA classes I and II), serum aldosterone levels do not exhibit an increase unless the use of potent loop diuretics leads to a reduction in intravascular volume and renal hypoperfusion, thereby triggering the activation of the

renin-angiotensin-aldosterone system.[11,12] Secondary hyperaldosteronism, along with the escalated administration of diuretics for patient relief in this advanced stage, leads to the development of secondary hyperparathyroidism. This condition is believed to be triggered by the heightened excretion of calcium and magnesium in both urine and feces.[13] Conversely, the phenomenon known as the calcium paradox involves the promotion of intracellular calcium overload, including within the mitochondria, by parathyroid hormone (PTH). This process leads to the destruction of these cellular organelles, ultimately resulting in cardiomyocyte necrosis and subsequent release of troponins. There is a significant body of evidence in individuals diagnosed with chronic kidney disease that demonstrates a strong association between the deterioration of renal function and the occurrence of unfavorable cardiovascular events, such as cardiovascular mortality.According to a case report, the performance of parathyroidectomy in a patient with chronic kidney disease and left ventricular dysfunction resulted in a significant enhancement of left ventricular ejection fraction (LVEF) [15].[16] This association implies a potential correlation between elevated levels of circulating parathyroid hormone (PTH) and the occurrence of cardiovascular morbidity and mortality. The progression of heart failure (HF) results in the development of cardiac cachexia, which is characterized by the loss of soft tissue and bone mass in the later stages of the disease. Cardiac cachexia is an additional clinical criterion employed for the identification of advanced heart failure. The data presented consistently demonstrate a negative correlation between body mass index and NYHA class, indicating that as NYHA class increases, there is a decrease in body mass index. The phenomenon of intracellular calcium overloading, which is mediated by PTH, is commonly referred to as the calcium paradox. This condition has been observed to induce oxidative stress in various tissues. The occurrence of oxidative stress in peripheral mononuclear cells triggers signal transduction, transcription, and activation processes, resulting in an upregulation of cytokines and chemokines.[17] The role of interleukin-6 and tumor necrosis factor-α in the pathogenesis of soft tissue and bone loss in advanced congestive heart failure has been extensively documented.[18,19] The occurrence of apoptosis in myocytes of the myocardium and skeletal muscle is induced by oxidative stress within the cells.Secondary hyperparathyroidism has been identified as the underlying cause of osteopenia and osteoporosis observed in a significant number of patients with advanced heart failure. Recent research has demonstrated that the administration of vitamin D and calcium carbonate as dietary supplements can enhance ventricular function in individuals of African-American descent who have heart failure.BNP has been extensively utilized as a biomarker for the purpose of establishing the diagnosis and predicting the prognosis of individuals with heart failure.[22,23] The level of blood in the ventricles is influenced by the loading status. Parathyroid hormone (PTH) is known to be released following a complex cascade of physiological processes within the human body, and its secretion is not influenced by the individual's volume status.[24,25] In the present investigation, a significant association was observed between parathyroid hormone (PTH) and brain natriuretic peptide (BNP) concentrations. It is suggested that parathyroid hormone (PTH) may offer additional insights in the identification of advanced heart failure (HF), in addition to the conventional indicators of New York Heart Association (NYHA) functional class and B-type natriuretic peptide (BNP) levels.

The findings of this study indicate that patients with advanced heart failure exhibited a notable decrease in creatinine clearance. Renal dysfunction, as indicated by elevated serum creatinine levels, is frequently observed in a significant number of patients who have advanced heart failure. This dysfunction is primarily attributed to renal hypoperfusion. The predictive significance of serum creatinine has been demonstrated in populations with heart failure.[26] Our study excluded patients who had evident renal dysfunction due to the possibility of an interaction. The findings of our study indicate that elevating the concentration of parathyroid hormone (PTH) may lead to the development of advanced heart failure (HF) in individuals with mild renal insufficiency. This is noteworthy considering the prognostic implications of this condition; however, the impact on cardiovascular mortality remains uncertain.[27]

LIMITATIONS OF THE STUDY

The limited patient enrollment in this study precludes the extrapolation of cut-off points, necessitating further research to determine the optimal cut-off point for advanced heart failure. Due to technical limitations, we were unable to directly measure aldosterone levels alongside parathyroid hormone (PTH). However, we attempted to establish an indirect association between PTH and aldosterone by assessing the NYHA functional class. Due to the potential for interaction, a considerable number of patients who were previously prescribed aldosterone blockers were excluded from the study. Specifically, individuals classified as NYHA classes III and IV were primarily excluded. The primary objective of this study was to investigate the potential correlation between parathyroid hormone (PTH) and aldosterone. It is worth mentioning that nearly all patients exhibiting NYHA class III to IV symptoms were prescribed an aldosterone blocker subsequent to the initial outpatient visit. In addition, individuals who experienced recent decompensation and those who were currently experiencing acute (or subacute) decompensation of heart failure were not included in the study due to difficulties in accurately categorizing

patients into a single NYHA class and the potential for confounding effects from fluctuating hemodynamics. Furthermore, the exclusion of patients undergoing up-down titration of heart failure medications was justified due to the potential confounding effect of symptomatic status.

CONCLUSION

we concluded that the serum parathyroid hormone (PTH) levels has the potential to offer additional valuable insights and serve as a straightforward biomarker approach for classifying individuals with advanced heart failure (HF) who exhibit elevated PTH levels. This method enables swift risk stratification in this particular patient population.

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