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# Effect of Vitamin D on Clinical Outcomes of Heart Failure: A Prospective Follow-Up Study in Bangladesh

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**Abstract** **Original Research Article**

Heart failure (HF) remains a leading cause of morbidity and mortality worldwide, serum vitamin D has emerged as a potential regulator of cardiovascular health. This study aimed to evaluate the relationship between serum vitamin D levels and clinical parameters in patients' with heart failure, as well as its influence on clinical outcomes. A prospective, follow-up study on patients of HF at two tertiary cardiac centers of Dhaka, assessing serum vitamin D levels alongside risk factors, clinical characteristics, hospitalization and mortality. Patients were stratified based on vitamin D levels low <20ng/dl) or high (>20ng/dl) to explore potential correlations with serum biomarkers and disease outcome. The mean age in low vitamin D arm (n=48) was 56.37±11.49 vs in high vitamin D arm (n=72) was 54.56±10.11, males consisted of 58.3% & 89.9% in arm A & B. 77.1% vs 77.8% of the patients in low and high vitamin D were non-diabetics, the effect of smoking was significant (p=0.042) within the arms. Serum CRP, BNP, PTH were remarkably higher (p <0.05) in low vitamin D arm moreover, β-blockers and loop diuretics were more frequent (p <0.05). Low serum vitamin D levels exhibited increased hospitalization, hospital stay, adverse effects and mortality (p value<0.001). This study presents a potential association between vitamin D deficiency and corresponding clinical and biochemical profiles in heart failure patients. These findings reinforce the growing hypothesis that vitamin D may play an active role in cardiovascular pathophysiology, potentially influencing disease progression and outcomes.

**Keywords:** Vitamin D, Heart Failure, Hospitalization, Mortality, BNP, CRP, PTH, Clinical Outcome.



## 1.INTRODUCTION

Heart failure (HF) is the terminal pathway for a diverse group of cardiovascular diseases and a leading cause of hospitalization and mortality worldwide. Defined as the heart's inability to pump sufficient blood to meet the metabolic demands of peripheral tissues, HF is not only a progressive and deteriorating condition but also a global public health crisis. Current epidemiological data estimate that over 64 million individuals are living with heart failure globally, with rising prevalence attributed to aging populations, urbanization, and the growing burden of cardiometabolic risk factors. Despite numerous therapeutic advances in pharmacologic and device-based treatments, the prognosis of HF remains insufficient, with five-year mortality rates comparable to many malignancies. [Tanai E & Frantz S, 2016, Murray CJ *et al.*, 2020, Savarese G & Lund LH, 2017, Benjamin EJ *et al.*, 2019]

The pathophysiology of HF is multifactorial, involving a complex interplay of neurohormonal activation, hemodynamic overload, inflammation, oxidative stress, and adverse cardiac remodeling.

[Solomon SD *et al.*, 2005] Recently, considerable attention has been drawn to the potential role of micronutrients, particularly vitamin D, in cardiovascular health. Traditionally recognized for its role in calcium-phosphorus homeostasis and skeletal health, vitamin D has emerged as a pivotal regulator of the cardiovascular system, influencing endothelial function, vascular tone, myocardial contractility, and inflammatory responses. [Pilz S *et al.*, 2008, Zittermann A *et al.,* 2007]

Low serum levels of vitamin D is a condition highly prevalent among HF patients which has been consistently associated with increased incidence, severity, and adverse outcomes in heart failure. [Zittermann A *et al.*, 2003, Kim DH *et al.,* 2008] The mechanistic link between hypovitaminosis D and HF is multifaceted. Vitamin D deficiency contributes to myocardial hypertrophy, fibrosis, and impaired contractility through dysregulation of the renin-angiotensin-aldosterone system (RAAS), endothelial dysfunction, heightened systemic inflammation, and increased oxidative stress all of which are well-established contributors to HF progression. [Artaza JN & Norris KC, 2009, Wang TJ *et al.*, 2008] Additionally, low vitamin D levels impair calcium handling in cardiac myocytes, potentially compromising myocardial performance and physiological stability of electrolytes. [Gouni-Berthold I *et al.*, 2009]

Apart from its close association with disease development, vitamin D supplementation has demonstrated potential cardiovascular benefits by modulating cardiac biomarkers. Several studies have reported favorable effects of vitamin D on markers such as N-terminal pro-brain natriuretic peptide (NT-proBNP), high-sensitivity C-reactive protein (hs-CRP), and troponin, suggesting a role for vitamin D not only as a preventive agent but also as an adjunct in the clinical management of HF. [Dalbeni A *et al.,* 2014, Boxer RS *et al.*, 2013] These observations highlight the fascinating possibility that vitamin D status could influence both the pathogenesis and the clinical course of heart failure. In this context, the present study aims to investigate the relationship between vitamin D levels in patients with heart failure, with particular focus on its impact on clinical parameters outcomes. Proper understanding of the association could pave the way for novel preventive and therapeutic strategies targeting an often-overlooked yet modifiable risk factor in cardiovascular disease.

## 2. MATERIALS AND METHODS

### Patient Selection

This prospective observational study was conducted from January 2021 to June 2024 in two tertiary care hospitals in Bangladesh. The study participants were recruited from the Cardiology, Outpatient Department and CCU of Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM), as well as the Cardiology Department of Ibrahim Cardiac Hospital & Research Institute (ICHRI). Successive patients (age >18 years) diagnosed with HF (ejection fraction <50%) & CAD were included in the study. Patient enrollment was performed between January 2021 and July 2022 to minimize any seasonal variation in vitamin D levels.

**Exclusion Criteria:**

3. Patients with decompensation of HF in the last 4 months, patients with New York Heart Association (NYHA) functional capacity class IV, and patients with atrial fibrillation
4. Patients with New York Heart Association (NYHA) functional capacity class IV, and patients with atrial fibrillation
5. Patients with a history of gastrectomy, intestinal malabsorption, primary or secondary hyperparathyroidism, any disease relevant to bone metabolism, cancer or chronic kidney disease (eGFR <60 ml/min/1.73 $m^2$)
6. Patients using alcohol, exogenous vitamin D, antiepileptic medication or medications with effects on calcium metabolism
7. Patients with abnormal liver function (elevated liver enzymes more than three times the upper limit of normal), anemia (<120 g/L in women, <130 g/L in men), hyponatremia (<135 mmol/L) in the baseline or follow-up laboratory tests, or deterioration in renal function (>26.5mmol/L increase in creatinine level) during follow-up
8. Patients who changed or stopped using their HF medication
9. Patients who underwent revascularization procedures.

Purposive sampling technique was used in this study according to the inclusion and exclusion criteria. A group of 150 patients was included in the recruitment period. During follow-up, 30 patients were excluded from the study, and these patients were not included in the statistical analysis of the data. The final study population consisted of 120 patients. Following a subject recruitment, a semi-structured questionnaire specifically developed for this study was used to gather information on their detailed socio-demographic factors, clinical history and previous medical records, which were compiled in a data collection sheet. The questionnaire consisted of questions related to a) socio-demographic characteristics b) behavioral risk factors c) history of pre-existing diseases. All relevant investigations were done later and their corresponding results were noted.

### Clinical Parameters

All blood and serum samples were collected and stored in sterilized containers. Diabetes mellitus was defined as fasting blood glucose level >7 mmol/L, or the use of insulin or oral hypoglycemic agent. Coronary artery disease was assessed from patients' medical reports. Patient's total history of cardiac events and hospital stay was recorded and current anti-hypertensive

medication was also listed from previous medical records. At presentation, blood samples were collected for routine biochemical tests after 12 hours of fasting and BNP, CRP, PTH levels were measured. Vitamin D levels were measured using the high-performance liquid chromatography method, values <20 nmol/L were considered low and values >20 nmol/L were considered high vitamin D. Patients were classified into two groups based on their vitamin D levels: Arm A with vitamin D levels <20 nmol/L and Arm B with vitamin D levels >20 nmol/L. All participants gave their written informed consent. The study was approved by an institutional ethics committee.

**Follow-Up**

All the patients were followed up for 2 years or till death. Patients' follow-up data were collected semiannually from patients' medical records, periodic patient examination in the outpatient setting or patient telephone interviews. Events considered were hospitalization, duration of hospital stay and overall death. Hospitalization was defined as inpatient treatment for at least one day due to decompansation of HF. Overall deaths were defined as all deaths from any natural cause.

**Statistical Analysis**

Variables are expressed as frequencies, percentages (%), means (±standard deviation) and medians (interquartile range), as appropriate. Categorical variables were compared by the Pearson Chi-square test. Inter-group comparisons of continuous variables were performed using Student's t-test. All significance tests were two-sided and used p-values of <0.05; those within the 95% confidence interval were considered significant. All analysis was done using Statistical Package for Social Sciences (SPSS) version 26 software.

## 3. RESULTS

**Table 1: Sociodemographic characteristics of the study population (n=120)**

| Variable | Low Vit D (≤20 ng/ml) n=48 | High Vit D (>20 ng/ml) n=72 | Total n=120 | P value |
|---|---|---|---|---|
| Age (years) | | | | |
| 25-35 | 2 (4.20%) | 2 (2.78%) | 4 (3.33%) | 0.781 |
| 35-45 | 7 (14.58%) | 12 (16.67%) | 19 (15.83%) | |
| 45-55 | 15 (31.25%) | 29 (40.28%) | 44 (36.67%) | |
| 55-65 | 15 (31.25%) | 20 (27.78%) | 35 (29.17%) | |
| >65 | 9 (18.75%) | 9 (12.50%) | 18 (15%) | |
| Mean age (years) | 56.37±11.49 | 54.56±10.11 | 55.28 ± 10.67 | |
| Gender | | | | |
| Male | 28 (58.33%) | 59 (81.94%) | 87 (72.50%) | **0.005** |
| Female | 20 (41.67%) | 13 (18.06%) | 33 (27.50%) | |
| Occupation | | | | |
| Business | 13 (27.08%) | 15 (20.83%) | 28 (23.33%) | **0.001** |
| Service | 6 (12.50%) | 13 (18.06%) | 19 (15.83%) | |
| Day labour | 1 (2.08%) | 0 | 1 (0.83%) | |
| Housewife | 19 (39.58%) | 12 (16.67%) | 31 (25.83%) | |
| Farmer | 2 (4.17%) | 24 (33.33%) | 26 (21.67%) | |
| Other | 7 (14.58%) | 8 (11.11%) | 15 (12.50%) | |

Table 1 elaborates on the sociodemographic characteristics of 120 patients suffering from heart failure. The majority of the patients belonged to the 45-55 and 55-65 age groups in both arms, where 31.3% of them were in both the 45-55 & 55-55 year age group among low vitamin D arm on the contrary, 40.3% & 27.8% in 45-55 & 55-65 year age group. The mean age in low vitamin D arm was 56.37±11.49 vs 54.56±10.11 in high vitamin D arm. Mean age was 55.28 ± 10.67 years, fraction of male was higher in both arms of low & high vitamin D bearing 58.3% & 89.9% patients. While a large proportion of low vitamin D patients were housewives (39.5%), farmers comprised of greater percentage in the high vitamin D arm.

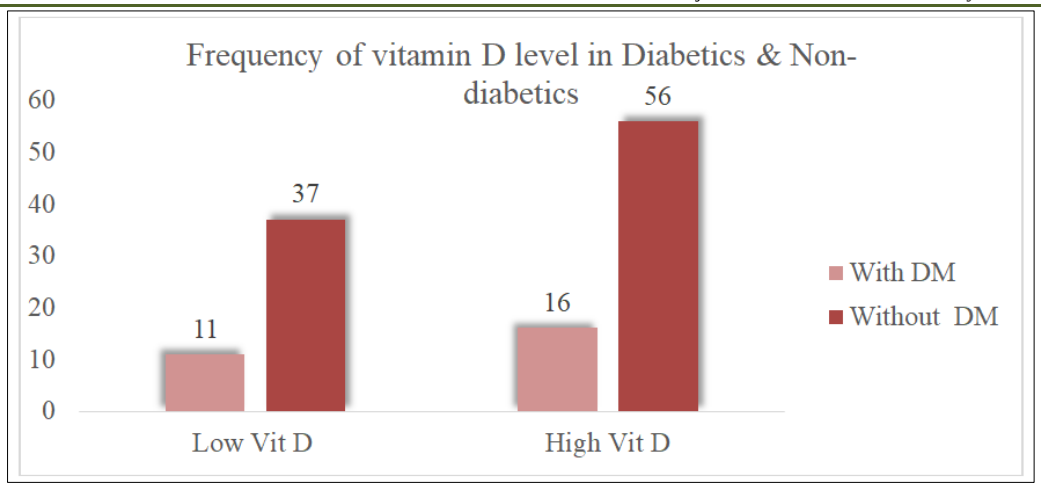


**Figure 1: Fraction of participants with or without diabetes mellitus having low or high serum vitamin D levels.**

The figure 1 illustrates the distribution of patients with or without diabetes mellitus within the two arms of low & high vitamin D. It is noticed that among patients with low vitamin D, 11 (22.9%) and 37 (77.1%) of the patients were diabetics & non-diabetics respectively. On the contrary, 16 (22.2%) and 56 (77.8%) of them were with and without DM within the high vitamin D group.

**Table 2: Etiological parameters and clinical manifestation of the population (n=120)**

| Variable | Low Vit D n=48 | High Vit D n=72 | P value | RR |
|---|---|---|---|---|
| Etiological factors | | | | |
| Smoking | 26 (54.2%) | 52 (72.2%) | **0.042** | 0.455 (0.211-0.979) |
| Dyslipidemia | 20 (41.7%) | 36 (50%) | 0.370 | 0.714 (0.342-1.492) |
| Sedentary lifestyle | 36 (75%) | 46 (63.9%) | 0.200 | 1.696 (0.753-3.816) |
| Family history of IHD | 19 (39.6%) | 34 (47.2%) | 0.409 | 0.732 (0.349-1.536) |
| Obesity | 16 (33.3%) | 27 (37.5%) | 0.641 | 0.833 (0.387-1.794) |
| Clinical manifestations | | | | |
| Chest pain | 48 (100%) | 72 (100%) | | |
| Breathlessness | 43 (89.6%) | 57 (79.2%) | 0.134 | 2.263 (0.763-6.710) |
| Palpitation | 16 (33.3%) | 17 (23.6%) | 0.243 | 1.618 (0.720-3.636) |

Table 2 shows the various etiological factors and clinical symptoms of HF. Significant effect of smoking (p = 0.042) was evident within the two arms, in addition, dyslipidemia (41.7% and 50%) & sedentary lifestyle (75% and 63.9%) were also prominent risk factors among the patients with HF.

Chest pain was common among all patients and breathlessness was observed in 89.6% in arm A and 79.2% in arm B.

**Table 3: Clinical characteristics of the population based on vitamin D levels (n=120)**

| Variable | Low Vit D (≤20 ng/ml) n=48 | High Vit D (>20 ng/ml) n=72 | P value |
|---|---|---|---|
| TC (mg/dl) | 190.88 ± 53.20 | 189.18 ± 48.91 | 0.858 |
| TG (mg/dl) | 158.06 ± 88.16 | 159.10 ± 106.78 | 0.956 |
| HDL (mg/dl) | 38.98 ± 5.53 | 38.11 ± 6.26 | 0.437 |
| LDL (mg/dl) | 120.81 ± 40.66 | 118.81 ± 39.52 | 0.788 |
| Troponin I | 21.14 ± 17.32 | 17.98 ± 16.96 | 0.324 |
| HTN | 16 (33.3%) | 20 (27.8%) | 0.515 |
| CRP (nmol/L) | 51.03 ± 9.50 | 35.85 ± 8.45 | **0.01*** |
| BNP (ng/L) | 85 ± 11.04 | 47 ± 6.97 | **<0.001*** |
| PTH (ng/L) | 68 ± 7.56 | 52 ± 5.65 | **<0.001*** |
| β-blocker | 40 (83.3%) | 49 (68.1%) | **0.006*** |
| Loop diuretics | 41 (85.4%) | 53 (73.6%) | **0.048*** |

Results of the biochemical parameters revealed that triglyceride and LDL levels are slightly elevated whereas HDL values are lowered within the two arms in Table 3. Arm a demonstrated significantly elevated CRP, BNP, and PTH compared to Arm B ($p < 0.05$ for all). A comparison of treatment approaches between the groups revealed that β-blockers ($p = 0.006$) and loop diuretics ($p = 0.048$) were utilized more frequently in Arm A.

**Table 4: Cardiac risk factors, hospitalization and mortality of the patients (n=120)**

| Variable | Low Vit D (≤20 ng/ml) n=48 | High Vit D (>20 ng/ml) n=72 | P value |
|---|---|---|---|
| Cardiogenic shock | 21 (43.8%) | 23 (31.9%) | 0.189 |
| Arrythmia | 10 (20.8%) | 9 (12.5%) | 0.221 |
| Hospitalization | 11 (22.9%) | 3 (4.2%) | **0.002*** |
| Mean hospital stay | 10.07 ± 1.91 | 2.17 ± 1.45 | **<0.001*** |
| Overall death | 8 (16.7%) | 2 (2.7%) | **<0.001*** |
| Adverse effects | 15 (31.3%) | 6 (8.3%) | **<0.001*** |

As shown in Table 4, the incidence of cardiogenic shock was higher (43.8%) among participants, of arm A. Additionally, hospitalization rates in arm A with 22.9% (n=11) against 4.2% in arm B (n=3) were significantly elevated in the lower vitamin D group in addition, the average duration of hospital stay was remarkably higher in arm A both with a p-value of <0.05. Moreover, both mortality and adverse events were notably more frequent in arm A.

## 4. DISCUSSION

This prospective, observational, follow-up study was conducted over a period of three and a half years at two renowned, specialized cardiac institutions in Dhaka namely BIRDEM and Ibrahim Cardiac Hospital & Research Institute. The primary objective of this study was to observe the effect of serum vitamin D levels on the patients of HF. Furthermore, the impact on clinical parameters, hospitalization and mortality was also assessed in this study.

Our findings indicate that HF was more prevalent among the elderly population, especially among the age groups of 55-65 years and 45-55 years. These two age classes collectively represent more than half of the population. The mean age in low vitamin D arm in our study was 56.37±11.49 years while 54.56±10.11 years in high vitamin D arm, homogenously the mean age was 56.2±6 years in vitamin D insufficient against 54.4±9 years in vitamin D sufficient group in a similar study. Male domination was evident in our research particularly in the high vitamin D arm (90%) which is consistent with the aforementioned study. [Lopes MR *et al.*, 2014] Most of the vitamin D insufficient patents were housewives whereas vitamin D sufficient ones were farmers.

A lion's share of patients were non-diabetic (70%) within both the arms according to our results harmonious to that of previous studies with half of the population without DM. [Lopes MR *et al.*, 2014, Gotsman I *et al.*, 2012] Between the two arms effect of smoking as an etiological factor was statistically significant (p=0.042) moreover, sedentary lifestyle along with dyslipidemia were notable threats of concern in both the arms according to this research. Widespread presence of sedentary lifestyle was observed among low vitamin D patients is in line with prospective tertiary center studies. [Anderson JL *et al.*, 2010, Ding N *et al.*, 2022] The most prominent symptoms of HF was found to be chest pain and breathlessness, a fraction of patients had suffered from cardiogenic shock with a higher percentage in arm B.

Heart failure is a progressive and chronic condition that typically develops over an extended period, which may explain its higher prevalence among older adults. Age-related physiological changes, combined with the cumulative burden of cardiovascular risk factors, contribute to the increased susceptibility of this population to HF. Males are more prone to attend the hospital and hence timely diagnosed with chronic conditions like HF, women on the other hand, tend to hesitate to express their initial symptoms until later stage. Additionally, lifestyle habits such as smoking were found to be less prevalent among female participants, which may partially mitigate their cardiovascular risk compared to men. Furthermore, a significant proportion of patients with vitamin D insufficiency were identified as housewives, whereas those with sufficient vitamin D levels were predominantly engaged in farming. This finding highlights the crucial role of occupational sunlight exposure in the endogenous synthesis of vitamin D, particularly in regions where outdoor labor correlates strongly with higher serum vitamin D levels.

Moreover, the occupational distribution suggested that a large number of patients seeking care at the hospital may belong to lower socioeconomic backgrounds, which might also explain the relatively low prevalence of diabetes in the studied cohort. Nevertheless, sedentary lifestyles were widespread, and a considerable subset of patients exhibited dyslipidemia. Smoking was notably prevalent in this population, representing a significant modifiable risk factor that could exacerbate the progression of heart failure.

In our study, patients with lower serum vitamin D levels demonstrated significantly elevated concentrations of brain natriuretic peptide (BNP), C-reactive protein (CRP), and parathyroid hormone (PTH). Furthermore, the use of β-blockers and loop diuretics was notably more frequent in this group, likely reflecting a more advanced stage of heart failure and greater symptom burden. These patients also experienced a markedly higher rate and extended duration of hospitalization, alongside an increased incidence of mortality and adverse events. Vitamin D deficiency is associated with dysregulation of the renin-angiotensin-aldosterone system (RAAS), impaired myocardial contractility, and endothelial dysfunction, all of which can exacerbate heart failure (HF) progression. Elevated BNP levels may suggest worsened cardiac wall stress, while increased CRP reflects underlying systemic inflammation both of which are amplified in vitamin D insufficiency. High PTH levels may result from secondary hyperparathyroidism induced by vitamin D deficiency, further contributing to myocardial remodeling and dysfunction. [Ustundag Y *et al.*, 2024, Islam H *et al.*, 2024, Islam H *et al.*, 2024] Additionally, lower vitamin D levels are linked to reduced exercise tolerance and increased fluid retention, potentially explaining the greater reliance on β-blockers and diuretics. The cumulative effect of these physiological disruptions likely accounts for the higher morbidity, hospitalization rates, and mortality observed in the low vitamin D group. [Mann MC, 2015] The study also demonstrated that patients with vitamin D deficiency tended to experience longer hospital stays and higher mortality rates, reinforcing the potential link between suboptimal vitamin D status and adverse clinical outcomes in heart failure. Given the widespread prevalence of vitamin D deficiency and its observed association with poorer outcomes, routine assessment and correction of vitamin D levels as well as benefits of vitamin supplementation should be considered as part of a comprehensive management strategy for heart failure. Further prospective studies are warranted to clarify the role of vitamin D optimization in improving long-term outcomes in this vulnerable population.

### Limitations

This study acknowledges numerous factors that may restrict its impact. The inadequate sample size and lack of control group limits establishment of a causal relationship. The type of sampling may also lead to selection bias. Lack of proper follow-up and survival data restricts the scope of this this study. Future longitudinal and interventional studies are required to explore whether vitamin D supplementation could confer clinical benefits in HF management.

## CONCLUSION

The findings of this prospective study highlights a significant association between low serum vitamin D and BNP, CRP, PTH levels in patients with heart failure. Vitamin D insufficiency was correlated with multiple hospitalizations, prolonged hospital stays, and elevated mortality rates. These observations suggest that suboptimal vitamin D status may serve as a modifiable risk factor that could influence both the clinical course and prognosis of heart failure patients. Further large-scale, randomized controlled trials are required to confirm whether vitamin D supplementation can improve morbidity and mortality outcomes in this patient population.

**Conflict of Interest:** The authors declare no conflict of interest.

### Abbreviations

BNP: b-type natriuretic peptide
CAD: Coronary artery disease
CRP: C-reactive protein
DM: diabetes mellitus
HDL: High density lipoprotein
HF: Heart Failure
HS: Hospital stay
hs-CRP: high-sensitivity C-reactive protein
HTN: Hypertension
IHD: Ischemic heart disease
LDL: Low density lipoprotein
NT-proBNP: N-terminal pro-brain natriuretic peptide
PTH: parathyroid hormone. B
RAAS: renin-angiotensin-aldosterone system
TC: Total Cholesterol
TG: Triglyceride

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