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Association of Hypocalcemia with In-Hospital Outcomes in Patients with Heart Failure

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Author`s Contribution

[1,4,5] Substantial contributions to the conception or design of the work; or the acquisition, analysis, [2]Proof reading, critical revision of the manuscript for important intellectual content, [3]Statistical Analysis, [6]Active participation in active methodology

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ABSTRACT

Objective: To determine the association of hypocalcemia with in-hospital outcomes in terms of in-hospital mortality in patients with heart failure.

Methodology: This descriptive Study was done at department of Cardiology, LUMHS, Jamshoro, from March 2022 to March 2023. Patients aged 18 to 80 years old both genders, patients who were present with heart failure were included. Baseline investigations, including serum calcium levels, were performed, with hypocalcemia defined as serum calcium levels <8.7mg/dL. Patients were then categorized based on the presence or absence of hypocalcemia and assessed for in-hospital mortality. Data analysis was conducted using SPSS version 24.0.

Results: The mean age of the patients was 63.84 years with a standard deviation of 15.55 years and mean serum calcium level was 8.80 mg/dL. Among the patients, 69.4% were male and 30.6% were female. Among patients of heart failure, the in-Hospital mortality was 18.3%. The overall frequency of hypocalcemia in patients with heart failure was 19.40%. Among patients how died during hospital stay, 2.6% had hypocalcemia, while 16.8% were died without hypocalcemia, the p-value 0.316 indicated that the association of hypocalcemia was statistically insignificant (p-0.316). The P-values for gender and diabetes mellitus were significant (<0.05), indicating a correlation between these factors and hypocalcemia, while age and hypertension showed insignificant associations with hypocalcemia (>0.05).

Conclusion: In conclusion, hypocalcemia appears to be prevalent among patients with heart failure. However, study did not find a significant association between hypocalcemia and in-hospital mortality. Further well-controlled prospective trials are recommended to confirm the findings.

Key words: Calcium, Heart Failure, Hypocalcemia, Mortality.

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Introduction

Heart failure is a clinical syndrome caused by abnormalities in the structure or function of the heart in the myocardium, which leads to reduced ventricular filling or cardiac output.[1] Heart failure is one of the major causes of mortality worldwide.[1] It is recognized fundamentally as a heterogeneous condition, which varies in terms of its features as well as management among different individuals.[2] It is often complicated by kidney disease, thus leading to the development of cardio-renal syndrome. Furthermore, such patients are often given diuretics as part of treatment.[2] Such comorbid conditions lead to vascular calcification, electrolyte imbalance and electrical instability which increases the rates of morbidity and mortality in individuals with heart failure.[3] Among the electrolyte disturbances, decreased sodium levels and increased potassium levels in the serum have been considered major prognostic factors in patients with heart failure.[3] However, few reports are available on the effect

of calcium homeostasis in such patients.[4] homeostasis of calcium is thought to be affected by numerous factors such as intake of calcium, levels of parathyroid hormone, metabolism of bone, renal disease, and disturbances in the levels of vitamin D.[5] Calcium plays a crucial role in the contraction and relaxation of myocardial muscles.[6]

Hypocalcemia is thought to be associated with adverse prognostic outcomes in patients with heart failure as it is associated with systolic and diastolic dysfunction, prolonged QT interval and increased levels of parathyroid hormone, which is associated with high rates of mortality as a result of pump failure and arrhythmias in patients with heart failure.[7] In a study, it was found that in patients with heart failure, hypocalcemia was present in 50.4% of patients, whereas in another study, Miura et al. revealed that hypocalcemia was only present in 16.7%,[3] patients with heart failure and CKD was associated with cardiac arrest in 31.3% patients and with in-hospital mortality in 21.9% patients.[3] In another study, it was found to be associated with in-hospital mortality in 7.23% of patients compared to 3.59% in those with normal levels of serum calcium ($p<0.001$) and was associated with an increased average length of hospital stay i.e. 8.2 days compared to patients in which calcium levels were normal i.e. 5.34 days.[2] Numerous international studies have been conducted which revealed variable findings in terms of the frequency of hypocalcemia and outcomes related to it in patients with heart failure. However, no such study has been conducted so far in Pakistan. Hence, the aim of this research paper is to evaluate the prevalence of hypocalcemia in patients with heart failure and investigate its correlation with in-hospital outcomes, focusing specifically on in-hospital mortality. This study seeks to elucidate the importance of calcium levels as a prognostic indicator in individuals with heart failure, offering valuable insights for healthcare providers. Ultimately, the results of this study may assist clinicians in making informed decisions regarding the timely replenishment of electrolytes to reduce the morbidity and mortality rates associated with heart failure.

Methodology

This was a descriptive Study conducted at department of Cardiology, LUMHS, Jamshoro. Study duration was six months from March 2022 to March 2023. A sample of 268 patients was calculated, keeping a 95% confidence interval, 5% margin of error and the expected percentage of in hospital mortality with hypocalcemia in heart failure patients as 21.9%.[3] Non-Probability, Consecutive sampling technique was used. Patients aged 18 to 80 years old both genders, patients who were present with heart failure (fulfilled one major and two minor criteria according to Framingham heart failure criteria) were included. Patients presented with acute coronary syndrome (STEMI and NSTEMI), patients with renal failure, bone disorder, thyroid hormone disorder, hypoalbuminemia and patients with chronic liver disease and pulmonary embolism were excluded. The study was conducted following approval from the ethical review committee of Liaquat University of Medical Health Sciences, Jamshoro, Hyderabad. Patients were enrolled after providing written informed consent. Detailed demographic information, clinical history, and physical examinations were conducted for all patients, with the findings recorded on a pre-designed proforma. Following enrollment, patients were managed according to standard guidelines and their vital signs were monitored. Baseline investigations, including serum calcium levels, were performed, with hypocalcemia defined as serum calcium levels <8.7mg/dL. Patients were then categorized based on the presence or absence of hypocalcemia and assessed for in-hospital mortality, confirmed by a flat line on ECG during the current hospitalization. All findings were documented using the study proforma and subjected to statistical analysis. Data analysis was conducted using SPSS version 24.0.

Results

The mean age of the patients was 63.84 years with a standard deviation of 15.55 years. The mean serum calcium level was 8.80 mg/dL with a standard deviation of 1.36 mg/dL. Among the patients, 69.4% were male and 30.6% were female. Additionally, 44.8% of patients had diabetes mellitus, Hypertension was in 68.7% of patients. Regarding smoking status, 39.2% were smokers and 60.8% were non-smokers. The use of loop diuretics was reported in 48.5% of patients and 61.2% of patients were using ACE/ARB inhibitors. Table I

Table I: Demographic characteristics of the patients of patients with heart failure. (n=268)

Variable		Percentage%
Age		63.84±15.55 years
Serum Calcium Levels		8.80±1.36
Gender	Male	186(69.4%)
	Female	82(30.6%)
Diabetes Mellitus	Diabetic	120(44.8%)
	Non-Diabetic	148(55.2%)
Hypertension	Hypertensive	184(68.7%)
	Non-Hypertensive	56(31.3%)
Smoking Status	Smoker	105(39.2%)
	Non-Smoker	163(60.8%)
Use of Loop Diuretics	Yes	130(48.5%)
	No	130(48.5%)
ACE/ARB Inhibitors	Yes	164(61.2%)
	No	104(38.8%)

Among patients of heart failure, the in-Hospital mortality was 18.3%. (Figure 1) The overall frequency of hypocalcemia in patients with heart failure was 19.40%. (Figure 2) Among patients how died during hospital stay, 2.6% had hypocalcemia, while 16.8% were died without hypocalcemia, the p-value 0.316 indicated that the association of hypocalcemia was statistically insignificant (p-0.316). Table II

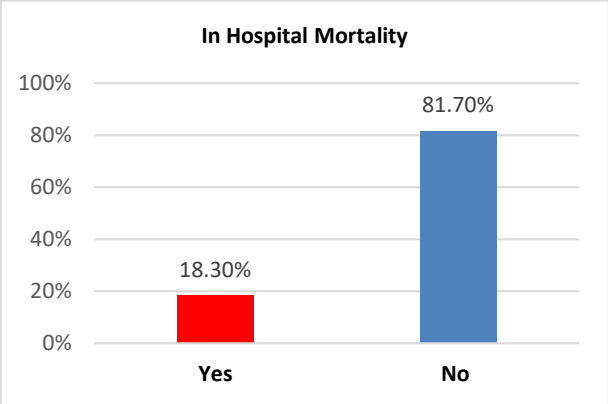

Figure 1. Frequency of in Hospital mortality in patients with heart failure. (n=268)

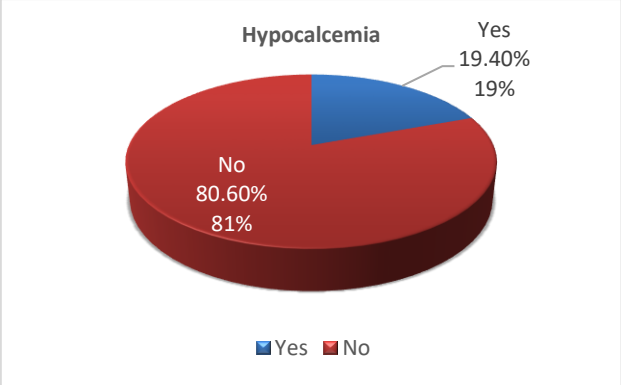

Figure 2. Frequency of hypocalcemia in patients with heart failure. (n=268)

Table II: Association of in-Hospital mortality with hypocalcemia. (n=268)

In Hospital Mortality	Hypoglycemia		P-value
	Yes	No	
Yes	7 (2.6%)	42 (15.7%)	0.316
No	45 (16.8%)	174 (64.9%)	

Applied Chi-Square test

Among individuals aged 18 to 60 years, 5.6% had hypocalcemia, while in the age group over 60, 13.8% patients were affected. Analysis by gender revealed that 9.3% of males and 10.1% of females had hypocalcemia. In terms of diabetes mellitus, 6.3% of diabetic individuals and 13.1% of non-diabetic individuals had hypocalcemia. Hypertension was associated with 14.2% of affected individuals by hypocalcemia. The P-values for gender and diabetes mellitus were significant (<0.05), indicating a correlation between these factors and hypocalcemia, while age and hypertension showed insignificant associations with hypocalcemia (>0.05). Table III

Table III: Hypocalcemia according to demographic characteristics and smoking status (n=268)

Demographic characteristics		Hypocalcemia		P-value
		Yes	No	
Age Group	18 – 60	15 (5.6%)	67 (25.0%)	0.760
	>60	37 (13.8%)	149 (55.6%)	
Gender	Male	25 (9.3%)	161 (60.1%)	0.0001
	Female	27 (10.1%)	55 (20.5%)	
Diabetes Mellites	Yes	17 (6.3%)	103 (38.4%)	0.051
	No	35 (13.1%)	113 (42.2%)	
Hypertension	Yes	38 (14.2%)	146 (54.5%)	0.444
	No	14 (5.2%)	70 (26.1%)	

Discussion

Heart failure (HF) stands as a predominant cause of mortality among the elderly in numerous countries worldwide. This condition, characterized by the heart's inability to pump blood effectively, leads to a range of symptoms and complications that significantly impact patients' quality of life. Interestingly, while hypocalcemia is considered a rare occurrence, it has been identified as a reversible underlying factor contributing to congestive heart failure.[8] This study aimed to assess the association between hypocalcemia and in-hospital outcomes, specifically in terms of in-hospital mortality, among patients with heart failure. A total of 268 patients were included in the analysis, with an overall mean age of 63.84 ± 15.55 years. These findings align closely with those of previous research. For instance, a study conducted by V et al.[9] reported a mean age of 75 ± 12 years for males and 72 ± 12 years for females. Similarly, another study documented a mean age of 74 years.[1] Additionally, Miura S et al. reported a mean age of 70.8 ± 12.4 years.[3] These comparisons highlight the consistency of our study's demographic characteristics with existing literature, providing context for the interpretation of our results. In our study, the gender distribution revealed that 186 (69.4%) participants were male, while 82 (30.6%) were female. This distribution is consistent with previous research findings. For instance, Shirakabe A et al.[1] reported a male predominance with 66.6% of participants

being male. Similarly, Miura S et al.[3] found a higher percentage of males, with 78.1%, compared to 21.9% females in their study. Our findings were also closed to the by the Fonseca AF et al[10] regarding age and gender. These comparisons provide additional context and support the generalizability of our study's findings regarding gender distribution among patients with heart failure.

In our study, hypocalcemia was identified in 52 (19.4%) patients. Among those who experienced in-hospital mortality, hypocalcemia was present in 7 (2.6%) cases, with a non-significant P-value of 0.316. Comparatively, Baqi DH et al.[11] underscored the importance of considering hypocalcemia as a potential contributor to heart failure in the diagnostic process for individuals presenting with congestive heart failure. Additionally, another case study highlighted hypocalcemia as a rare yet reversible factor associated with severe heart failure in uremic patients.[12] However, it is worth noting that while hypocalcemia can affect myocardial contractility, its role in causing congestive heart failure is infrequent.[13,14]

Moreover, studies have reported varying prevalence rates of hypocalcemia among patients with heart failure. For instance, one study found hypocalcemia in 50.4% of heart failure patients,[1] whereas Miura et al.[3] reported a lower prevalence of 16.7%. Additionally, in heart failure patients with chronic kidney disease (CKD), hypocalcemia was associated with a higher risk of cardiac arrest in 31.3% of cases (p=0.002) and in-hospital mortality in 21.9% of cases (p<0.001). These findings emphasize the need for further research to better understand the relationship between hypocalcemia and adverse outcomes in heart failure patients. In our study, hypocalcemia was found in 52 (19.4%) patients while in association with in-hospital mortality, hypocalcemia was found in 7 (2.6%) and the P value was found to be non-significant i.e. (P=0.316). In the comparison of this study Baqi DH et al[11] observed that the potential role of hypocalcemia in contributing to heart failure should be taken into account during the differential diagnosis of individuals presenting with congestive heart failure. According to findings from another case study, hypocalcemia may represent a rare yet reversible factor contributing to severe heart failure in patients with uremia.[12] On the other hand stated that the hypocalcemia is an uncommon but reversible factor associated with dilated cardiomyopathy, affecting either one or both ventricles. It reduces myocardial contractility, although the occurrence of congestive heart failure attributed to hypocalcemia is infrequent.[13,14] Furthermore in a study, it was found that in patients with heart failure, hypocalcemia was present in 50.4% of patients,[1] whereas in another study, Miura et al revealed that hypocalcemia was only present in 16.7%,[3] patients with heart failure and CKD was associated with cardiac arrest in 31.3% patients (p=0.002) and with in-hospital mortality in 21.9% patients (p<0.001). In another study, hypocalcemia was found to be linked with in-hospital mortality in 7.23% of patients, compared to 3.59% in those with normal serum calcium levels (p<0.001). Additionally, it was associated with a longer average length of hospital stay, with patients experiencing hypocalcemia staying an average of 8.2 days compared to 5.34 days for those with normal calcium levels (p<0.001).[2] Similarly, Shirakabe et al demonstrated that hypocalcemia in heart failure patients was associated with in-hospital mortality in 6% of cases, with a mean hospital stay of 27 days compared to 24 days for patients with normal calcium levels (p=0.014).[1]

Rozentryt P et al[15] also observed that irregular serum calcium levels are linked to a clinical response to maximizing treatment in patients with heart failure. Lin CS et al[16] also observed that the prompt identification of hypocalcemia as a triggering factor for congestive heart failure will facilitate the swift commencement of effective treatment and significantly enhance heart failure outcomes.

However, it's important to acknowledge the limitations of our study. Firstly, our study relied on retrospective data analysis, which may introduce bias and limit the ability to establish causal relationships. Secondly, the sample size in our study may have been insufficient to detect small but clinically significant differences in outcomes related to hypocalcemia. Additionally, the study did not account for potential confounding factors such as comorbidities or other electrolyte imbalances that could impact outcomes. Despite these limitations, our findings contribute to the growing body of evidence highlighting the association between hypocalcemia and adverse outcomes in heart failure patients. Further prospective studies with larger sample sizes and comprehensive multivariate analyses are recommended warranted to confirm these findings and elucidate the underlying mechanisms.

Conclusion

In conclusion, hypocalcemia was frequently observed in patients with heart failure. However, the study did not find a significant association between hypocalcemia and in-hospital mortality. Despite these results, it is important to note the limitations of our study, including sample size constraints and lack of control group. To further validate

our findings and elucidate the relationship between hypocalcemia and outcomes in heart failure patients, additional well-controlled prospective trials with larger sample sizes are recommended.

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