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*ORIGINAL ARTICLE*

# Effects of Spironolactone on Diastolic Function in Patients with Heart Failure with Preserved Ejection Fraction

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**Abstract**

***Background:*** *Management of heart failure with preserved ejection fraction (HFpEF) patients have become more challenging than systolic heart failure as there is no effective therapy for HFpEF. Mineralocorticoid receptor antagonists (MRA) like spironolactone inhibits the effect of aldosterone and may lead to improvement of left ventricular diastolic function.* ***Objective:*** *To evaluate the effects of spironolactone on diastolic function in patients with HFpEF.*

***Methods:*** *This Randomized control trial was conducted in the Cardiology Department of BSMMU from June, 2022 to May, 2023. A total of 54 patients of HFpEF who had NYHA class II-IV features of heart failure with echocardiographic evidence of diastolic dysfunction were randomly assigned into 2 groups. Then patients of spironolactone group were given spironolactone 25 mg/day in addition to standard risk factor control treatment and patients of control group were monitored with standard risk factor control treatment only. Baseline and after 6 months clinical and echocardiographic data were compared.*

***Results:*** *Total 52 patients completed the follow-up, among them 26 were in spironolactone group and 26 were in control group. Early mitral inflow velocity and mitral annular early diastolic velocity ratio (Average E/e') declined significantly after 6 months of spironolactone treatment (P value = .011). Septal e' and lateral e' were improved significantly in spironolactone group (P value = .003 and < .001 consecutively). Analysis of diastolic dysfunction grade showed that diastolic dysfunction grades remained quite unchanged (P value= .370).*

***Conclusion:*** *Spironolactone played a significant role in improvement of some of the parameters of diastolic dysfunction (like average E/e', septal and lateral e') although any significant effect on change of diastolic dysfunction grade was not observed in this study.* ***Keywords:*** *Spironolactone, Diastolic dysfunction, Average E/e', heart failure with preserved ejection fraction, HFpEF*

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**Highlights:**

1. Till now treatment of Heart failure with preserved ejection fraction is very challenging.
2. Diastolic dysfunction plays an important role for clinical manifestation symptoms in HFpEF.
3. Spironolactone showed improvement of average E/e', lateral e' and septal e' which are the important parameters of diastolic dysfunction.

## Introduction

Heart failure is one of the leading causes of morbidity and mortality throughout the world.[1] A significant proportion of patients with clinical heart failure have a preserved left ventricular ejection fraction (ejection fraction >50%) and suffer from predominantly diastolic dysfunction. Study shows that the prevalence of heart failure with preserved ejection fraction (HFpEF) is up to 55% in different countries which are increasing day by day.[2,3]

Typically, people with HFpEF present with normal left ventricular volume and function (EF> 50%) as well as signs of diastolic dysfunction. Functionally, diastolic heart failure (DHF) is characterized by impaired ventricular relaxation and reduced compliance of the ventricles.[4] As a result of impairment of diastolic filling there is

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inappropriate rise of left ventricular pressure after physiological volume loads which may manifest as heart failure.[5] Evidence shows that increased renal and local cardiac aldosterone production is related with these pathological changes.[6,7] Therefore, mineralocorticoid receptor antagonists (MRA) have been of particular interest in the management of HFpEF due to their effects on myocardial stiffness, extracellular matrix expansion, and vascular function, which are important factors in the pathogenesis of HFpEF.[5] However, clinical trials with spironolactone are few and the role of spironolactone in HFpEF treatment remains unclear.[8] The largest clinical trial with spironolactone named 'TOPCAT trial' showed that there was heterogeneity in response comparing subjects enrolled in the Americas as opposed to Russia and the Republic of Georgia.[9] Another important thing that for enrolment in that study objective evidence of diastolic dysfunction was not required. In fact, recruiting markedly heterogonous patient populations and selection of patients without objective evidence of LV diastolic dysfunction have previously been suggested as possible explanations for the neutral/negative outcomes of TOPCAT trial.[10] Thus, whether spironolactone truly improves the diastolic function is still in debate. So, this study was designed to see the effect of spironolactone on diastolic function in patients with heart failure with preserved ejection fraction.

**Objectives:**

General Objectives: To assess the effects of spironolactone on diastolic function in patients with heart failure with preserved ejection fraction.

Specific Objectives: To assess diastolic function in spironolactone group (study group) and control group during enrollment and after 6 months and then compare the effects in both groups.

**Methodology:**

Study Design:

This Randomized control trial was conducted in Department of Cardiology, University Cardiac Centre (UCC), Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka, Bangladesh from June, 2022 to May, 2023 after the approval of the protocol by Institutional review board. Patients who attended the outpatient or inpatient department of Cardiology, Bangabandhu Sheikh Mujib Medical University, Shahbag, Dhaka were enrolled by convenient and purposive sampling and then assigned into 2 groups randomly.

**Patient selection:**

**Inclusion Criteria**

Adults patients(age>18 years) with NYHA class II- IV features of heart failure with left ventricular ejection fraction (LVEF) ≥50% at rest along with echo-cardiographic evidence of diastolic dysfunction and raised BNP (≥35pg/ml) or NT- Pro BNP level (>125 pg/ml).

**Exclusion Criteria**

Significant renal dysfunction [creatinine>221 mmol/L (>2.5 mg/dL) or eGFR<30 mL/min/1.73 $m^2$ within past 2 weeks.],Serum potassium level > 5 mmol/L within past two weeks, systolic blood pressure < 90 mm Hg, acute coronary syndrome in past 90 days, HFpEF mimics like infiltrative/ restrictive cardiomyopathy, hypertrophic cardiomyopathy, significant valvular heart disease, or pericardial disease and non cardiac mimics like lung disease with or without cor pulmonale, known contraindications for spironolactone or known intolerance to therapy with MRA within last 3 months, who are on SGLT2 inhibitor therapy, concomitant severe systemic illness with life expectancy judged less than 6 months and patients who did not give consent to take part in this study.

**Study Procedure:**

A total of 54 patients of HFpEF who had New York Heart Association (NYHA) class II-IV features of heart failure with echocardiographic evidence of diastolic dysfunction were enrolled into the study after fulfilling inclusion & exclusion criteria and randomly allocated into 2 groups where 27 patients were included into control group and 27 patients were included into spironolactone group. HFpEF was diagnosed according to 2021, European Society of Cardiology guideline for diagnosis and management of chronic heart failure.[11] The purpose of the study was explained in detail to each subject & informed written consent was obtained. After getting consent, meticulous history was taken & relevant clinical examination was performed & recorded in predesigned structured proforma. During enrollment in the study 12 lead ECG, blood sugar, HbA1C, N-terminal pro b-type natriuretic peptide (NT-proBNP), S. creatinine, Serum electrolytes & estimated glomerular filtration rate (e GFR) were recorded. A resting echocardiography with detailed evaluation of the left ventricular diastolic function was done by GE VIVID E 9 echocardiography machine. Diastolic function was assessed according to the recommendations for the evaluation of left ventricular diastolic function by American Society of

Echocardiography (ASE) guideline published in 2016.[12] Then, the patients in the spironolactone group were given spironolactone 25mg daily in addition to standard risk factor control and patients of control group were given standard risk factor medication only. Patients were then monitored by serum creatinine & serum electrolytes at2 weeks, at 3 months and 6 months for development of hyperkalaemia (serum potassium ≥5.5 mmol/L) or significant renal impairment (S. creatinine ≥2.5 mg/dl). Patients were contacted on regular basis by telephone. If any problem aroused in between follow up schedule he/she was asked to contact with us or visit local registered physicians or hospital. After 6 months again history, clinical examination, detailed echocardiographic evaluation of diastolic dysfunction (by GE VIVID E9 machine) and outcome were noted in both groups. Finally among 54 cases, 1 patient from each group was dropped out from the study due to loss to follow-up and a total of 26 patients from control group and 26 patients from spironolactone group were assessed clinically and echocardiographically.

**Study outcome:**

Primary outcomes: Changes in echocardiographic parameters of LV Diastolic dysfunction- average E/e', septal e', lateral e', Left atrial (LA) diameter and Tricuspid regurgitation (TR) maximum jet velocity. Secondary outcome: Improvement of diastolic dysfunction grade.

**Statistical Methods**

Data were collected in a pre-designed format including history, clinical examination and investigations. Statistical analysis was conducted using SPSS 29.0 (Statistical Package for Social Science). Numerical variables were expressed as the mean and standard deviation, while categorical variables were described using frequency and percentages. The normality distribution of the data was assessed by Shapiro wilk test. Continuous variables were compared using either Student's t-test or Mann Whitney U test, depending on the normality distribution of the data. The categorical variables were analyzed using either the Chi-squared test or Fisher's exact test. In all cases, P-value of $< 0.05$ was considered as significant. Findings were expressed by graph and chart whichever was relevant.

**Results:**

Participants: During the period of June, 2022 to May, 2023 a total of 54 patients were enrolled and divided into 2 groups randomly and finally 52 patients completed the follow-up, among them 26 were in spironolactone group and 26 were in control group. The changes in echocardiographic parameters of diastolic dysfunction from baseline to the end of 6 months of follow up period were assessed & compared. Baseline characteristics of the patients are presented in the table I. Mean age of the patients were 61.2 years (SD, 5.4) among them 48.1% are female and 51.9% are male. There were no significant differences in between two groups.

**Table-I**

*Baseline characteristics of study population (N=52)*

| Characteristics | Total (N=52) | Control group ($n_1$=26) | Spironolactone group ($n_2$=26) | P value |
|---|---|---|---|---|
| Age,mean | 61.2 ± 5.4 | 59.0 ± 4.4 | 62.4 ± 6.1 | .094§ |
| Gender | | | | |
| Male | 27 (51.9) | 12 (46.2) | 15 (57.7) | .405Ø |
| Female | 25 (48.1) | 14 (53.8) | 11 (42.3) | |
| DM | 22 (42.3) | 10 (38.5) | 12 (46.2) | .575 Ø |
| HTN | 34(65.4) | 16 (61.5) | 18 (69.2) | .560 Ø |
| Dyslipidemia | 16 (30.8) | 8(30.8) | 8(30.8) | 1.00 Ø |
| Coronary artery disease | 12 (23.1) | 7(26.9) | 5(19.2) | .510 Ø |
| CKD | 9(17.3) | 4(15.3) | 5(19.2) | .714 Ø |
| AF | 4 (7.7) | 2(7.7) | 2(7.7) | .999 Ø |
| Hospitalization for Heart failure in past 12 months | 5 (9.6) | 2 (7.7) | 3 (11.5) | .638 Ø |
| Dyspnoea (NYHA Functional class) | | | | |
| II | 35(67.3) | 18(69.2) | 17(65.4) | .767 Ø |
| III | 17(32.7) | 8(30.8) | 9(34.6) | |

N=Total number of subject, $n_1$ and $n_2$= Number of the study subjects in each group, Data were expressed as Mean ±Standard Deviation and frequency with percentage, §P=Value Calculated using Independent t test, ØP= Value Calculated using Chi-square test, DM=Diabetes mellitus, HTN=Hypertension, CKD=Chronic kidney disease, AF=Atrial fibrillation, NYHA=New York Heart Association.

During enrollment 69.2% patients were taking ACEI/ARB there were no baseline significant differences of medications in between two groups (Table-II). The dosages of the drugs remained same throughout the duration of trial except diuretics which was changed according to the fluid status of the patient.

Echocardiographic parameters of diastolic dysfunction were taken at baseline and after 6 months of follow up where baseline measurements were consistent with HFpEF (Table-III). Table shows that after 6 months of treatment, average E/e' significantly reduced in spironolactone group (P value = .011) and where as septal e' and lateral e' increased significantly in spironolactone group(P value .003 and < .001 consecutively).TR jet velocity and LA volume index were also reduced after spironolactone treatment however the effects were not statistically significant.

Average E/e' reduced with spironolactone treatment from 16.82(SD, 1.8) to 15.27 (SD, 1.4) and increased in control group from 16.26 (SD, 2.2) to 16.52 (SD, 2.5) (Figure 1).After 6 months of treatment, average E/e' had significant difference between two groups (P = .011) although in the baseline data there was nosignificant difference between the groups (P = .067).

Similarly septal e' was improved in spironolactone group from 5.88 (SD, 0.5) to 6.77 (SD, 0.8) and in control group it was not changed significantly (Figure 2). Though there was no significant difference between the spironolactone group and control group at baseline (P= .568), however, it was observed that septal e' improved significantly (P =.003) in spironolactone group compared to control group after 6 months.

Lateral e' was also improved in spironolactone group from 7.7 (SD, 0.5) to 8.4 (SD, 0.5) and declined from 8.0 (SD,

**Table-II**

*Ongoing cardiac medications at baseline (N=52)*

| Medications | Total (N=52) | Control group ($n_1$=26) | Spironolactone group ($n_2$=26) | P value |
|---|---|---|---|---|
| ACEI/ARB | 36(69.2) | 17 (65.4) | 19 (73.1) | .548 |
| Beta blocker | 15(28.5) | 5(19.2) | 10(38.5) | .126 |
| Loop Diuretics | 17 (32.7) | 7(26.9) | 10(38.5) | .375 |
| Calcium channel blocker | 18(34.6) | 10(38.5) | 8(30.8) | .560 |
| Lipid lowering agent | 15(28.8) | 7(26.9) | 8(30.8) | .760 |
| Antiplatelet | 12 (23.1) | 7(26.9) | 5(19.2) | .510 |

N=Total number of subject, $n_1$ and $n_2$= Number of the study subjects in each group, ACEI=Angiotensin converting enzyme inhibitor, ARB=Angiotensin receptor blocker, Data were expressed as frequency with percentage, P Value Calculated using Chi-square test

Primary Outcome:

**Table-III**

*Echocardiographic parameters of diastolic function at baseline and after 6 months (N=52)*

| Parameters | Baseline | | | After 6 month | | |
|---|---|---|---|---|---|---|
| | Control Group ($n_1$=26) | Spironolactone Group ($n_2$=26) | P Value | Control group ($n_1$=26) | Spironolactone group ($n_2$=26) | P Value |
| Average E/e' | 16.26±2.2 | 16.82±1.8 | .067 | 16.52±2.5 | 15.27±1.4 | .011 S |
| Septal e' m/s | 6.0±.6 | 5.88±.5 | .568 | 6.04±.7 | 6.77±.8 | .003 S |
| Lateral e',m/s | 8.0±.8 | 7.7±.5 | .280 | 7.8±.5 | 8.4±.5 | .001S |
| TR jet velocity,m/s | 3.05±0.4 | 3.15±0.5 | .477 | 3.17±0.4 | 3.08±0.4 | .484 |
| LA volume index,ml/m2 | 35.08±1.8 | 35.42±1.9 | .219 | 35.63±1.5 | 35.37±2.1 | .703 |

N=Total number of subject, $n_1$ and $n_2$= Number of the study subjects in each group, E/e'=early mitral inflow velocity and mitral annular early diastolic velocity ratio, TR=Tricuspid regurgitation, LA=Left atrial, Data were expressed as Mean ± Standard deviation, S=Significant, P Value Calculated using 2 sided Mann –Whitney U tests (as the data were non parametric).

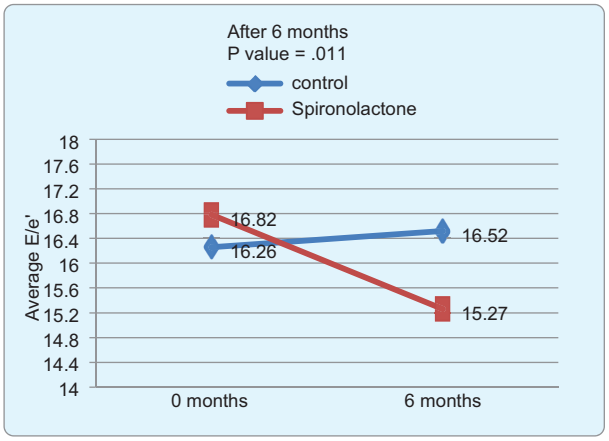


**Figure 1:** *Changing trend of Average E/e' over time*

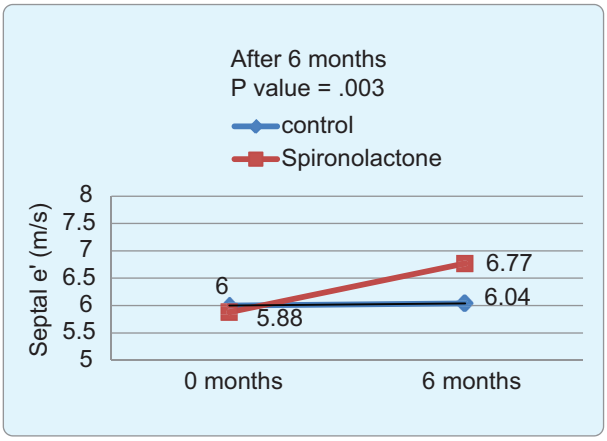


**Figure 2:** *Changing trend of Septal e' over time*

0.8) to 7.8 (SD, 0.5) in control group (Figure 3). After 6 months data analysis showed that there was a significant difference of lateral e' (P value < .001) though there was no difference at baseline data in between two groups.

Baseline and after 6 months diastolic dysfunction grades were shown in Table IV. Analysis revealed that diastolic dysfunction grades remained quite unchanged (P value = .492).

Changes of diastolic dysfunction grade in two groups after 6 months were analyzed (Table V). There was improvement of diastolic function grade in of about 16.7 % cases in spironolactone group in comparison to 8.3% cases in control group. Abo Figure 3. Changing trend of Lateral e' over time

ut 79.2 % cases in spironolactone group and 75.0% cases in control group, there were no grade change, where as increased percentage of patients in control group (16.7%) had worsening of diastolic dysfunction grade in comparison to spironolactone group (4.2%). Overall changes of diastolic dysfunction grade were not statistically significant ( p value = .370).

**Table-IV**

*Diastolic dysfunction grade at baseline and after 6 months (n=48)*

| Parameters | Baseline | | | After 6 month | | |
|---|---|---|---|---|---|---|
| Grading of Diastolic Dysfunction | Control Group (n=24*) | Spironolactone Group(n=24*) | P Value | Control group(n=24*) | Spironolactone group(n=24*) | P Value |
| I | 7(29.2) | 5(20.8) | .799 | 5(20.8) | 8(33.3) | .492 |
| II | 16(66.7) | 17(70.8) | | 18(75.0) | | 14(58.3) |
| III | 1(4.2) | 2(8.3) | 1(4.2) | 2(8.3) | | |

N=Total number of subject, $n_1$ and $n_2$= Number of the study subjects in each group, Data were expressed as frequency with percentage, P Value Calculated using Chi-square test,*Grading could not be done in 2 patients in each group due to AF.

**Secondary outcome:**

**Table-V**

*Change of diastolic dysfunction grade after 6 months (N=48)*

| Diastolic dysfunction grade | Control Group $n_1$=24 | Spironolactone Group, $n_2$=24 | p value |
|---|---|---|---|
| Improvement, n (%) | 2 (8.3) | 4 (16.7) | .370 |
| Static, n (%) | 18(75.0) | 19(79.2) | |
| Deterioration, n (%) | 4 (16.7) | 1 (4.2) | |

N=Total number of subject, $n_1$ and $n_2$= Number of the study subjects in each group, Data were expressed as frequency and Percentage, P Value Calculated using Fisher's exact test.

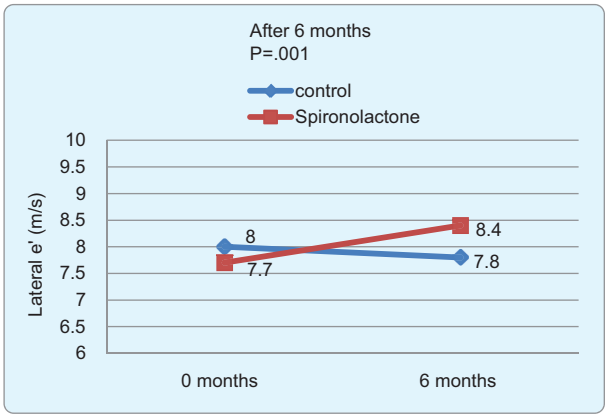


**Figure 3|:** *Changing trend of Lateral e' over time*

**Discussion:**

In this study we evaluated the effect of adding spironolactone in addition to recommended standard risk factor control in patients with heart failure and preserved ejection fraction. This study showed that significant reduction of average E/e' and improvement of septal e' and lateral e' occurred after spironolactone treatment which are the important non invasive parameters of diastolic function in patients with heart failure and preserved ejection fraction. Although parameters of diastolic dysfunction showed improvement but we didn't find any significant effect on change of diastolic dysfunction grade.

E/e' ratio had excellent specificity for identifying patients with elevated LV filling pressure in patients with HFpEF.[13] Nauta et al.[14] in 2018 found that E/e' value was associated with clinical outcome like mortality and/or composite endpoints in most of the studies, with a combined hazard ratio of 1.05 (1.03–1.06) per 1 unit increase. In the present study baseline average E/e' was 16.26(SD, 2.2) in control group and 16.82 (SD, 1.8) in spironolactone group which were consistent with elevated filling pressure. After 6 months average E/e' significantly reduced in spironolactone group (p value= .011), where as in control group E/e' had shown rising trend. Septal e' and lateral e' were also improved significantly in spironolactone group (P value = .003 and < .001 consecutively) though there was no significant difference at baseline. All these data indicated that treatment with spironolactone reduced LV filling pressure as well as improvement of both LV stiffness and relaxation which correlated with the result from Aldo-DHF trial[15] where they found that medial E/e' velocity ratio was significantly improved in spironolactone group (P value <0.001) along with improvement of medial e' velocity (P value= .002) in spironolactone group. A similar result was found in another study done by Kurrelmeyer et al. where significant reduction of lateral E/e' (P=.0001) and significant improvement of lateral e' (P=.003) were found after 6 months of spironolactone treatment.[16]

In this study we didn't find any significant improvement of other parameters of diastolic dysfunction like TR jet velocity and LA volume index.TR jet velocity was mildly reduced from 3.15(SD, 0.5) to 3.08(SD,0.4) in spironolactone group and increased in control group from 3.05(SD,0.4) to 3.17(SD, 0.4). Although there was mild improvement but the result was not statistically significant. But Kurrelmeyer et al. in their study found that pulmonary arterial systolic pressure (PASP) was significantly reduced after six months.[16]

LA volume index was also mildly reduced from 35.42 (SD, 1.9) to 35.37 (SD, 2.1) in spironolactone group where as it was mildly increased from 35.08 (SD, 1.8) to 35.63(SD, 1.5) in control group. After 6 months treatment the result was not statistically significant (P value= .703). This result was similar to the data found on Aldo- DHF trial[15] where P value for LA volume change was 51.

Regarding the change of diastolic dysfunction grade it was observed that a major portion of patients had no diastolic dysfunction grade change in both groups but percentages of patients who had improved diastolic dysfunction grade were more in spironolactone group (16.7 % in comparison to 8.3% in control group) and percentages of patients who had worsening of diastolic dysfunction grade were more in control group (16.7 % in comparison to 4.2% in spironolactone group), although the result was not statistically significant ( P value = .370).Though the parameters of diastolic dysfunction improved in spironolactone group but the changes of diastolic dysfunction were not significant which may be due to shorter duration of follow up. In Aldo DHF trial[15] they also found that diastolic dysfunction grade was not changed (P value= .10) after 12 months treatment with spironolactone.

Adverse effects were monitored by serum creatinine and serum electrolytes. Although renal function impairment was more in spironolactone group (23.1% vs. 7.7 %) but it was not statistically significant (p=.124). After 6 months follow up none of the patients from any group developed e GFR less than 30 ml/min/1.73m2. Although the interim follow up after 2 weeks and 3 months didn't show any increased serum potassium level above 5mmol/l but after 6 months a significant number of patients developed S potassium >5.0 mmol/l (P value .035) but none had serum potassium >5.5 mmol/l.

The present study should be interpreted in context of several limitations. The duration of the study was short which might have affected the expected outcome and might not reflective of exact scenario.

In conclusion, spironolactone had significant role in improvement of the non invasive parameters of diastolic dysfunction although any significant effect on change of diastolic dysfunction grade was not observed in this study. Further large scale, multicenter, randomized control study with longer duration of follow up is needed for detailed evaluation of effect of spironolactone on diastolic dysfunction in patients with heart failure and preserved ejection fraction.

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**Author Contributions:**
Concept and design: MTA, HH. Acquisition, Analysis and interpretation of data: MTA, SMNH, SKS, SNK, HNAR, AFMAA. Manuscript drafting and revising it critically: MTA, MM, FIK, TP, MKA, CMA. Approval of the final version of the manuscript: MTA, TP, MM, FIK, CMA, HH. Guarantor accuracy and integrity of the work: MTA, MM, MKA, FIK, HH.

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

**Ethical approval:**
Ethical approval for this study was granted by the Institutional Review Board of BSMMU (memo number : BSMMU/2022/3814)

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