

A Clinical Study of Heart Failure with Preserved Ejection Fraction in Patients at College of Medical Sciences, Teaching Hospital: A Tertiary centre from Central Nepal

Panjiyar RK*, Twayana RS**, Laudari S*, Gupta M*, Dhungel S*, Dubey L*, Subramanyam G*

* Department of Cardiology, College of Medical Sciences, Teaching Hospital Bharatpur, Nepal

** Respiratory Medicine, Sandwell and West Birmingham Hospitals, NHS Trust, Birmingham, United Kingdom

Abstract- Heart failure is growing epidemic condition and nearly half of the patients have preserved ejection (EF>50%). We aim to observe the baseline clinical characteristics and factors affecting hospital stay and outcomes after 28 days of follow up. An observational study was conducted among 200 patients who presented clinical features of heart failure according to Framingham Criteria, with Left ventricular EF \geq 50%, in College of Medical Sciences in the Department of Cardiology over a period of June 2015 to January 2017. Data were analyzed using IBM-SPSS 20.0 and descriptive and inferential analysis was performed.

Of 200 patients, 114(57%) were females and 86(43%) were males. The mean age of patient was 51.57(\pm 16.81) years with range of 20 to 89 years. The most common risk factors were Hypertension (78%) followed by obesity (55.5%), smoking (50%), dyslipidemia (48%), and Diabetes mellitus (48%). The most common presenting symptom was dyspnea (96%) followed by PND (55%), fatigue (51%) and cough. Most of the patients had Grade I Left ventricular diastolic dysfunction 84%. Associated regional wall abnormalities were found in 11%, pulmonary arterial hypertension in 57.5% and pericardial effusion in 10%. Total mortality in this study was (n=7)3.5% of them 2% within 24 hours of hospitalization and 1.5% during subsequent hospitalization within 30 days of discharge. We concluded the incidence of heart failure with preserved ejection fraction (HFPEF) was more in female. Hypertension was the most common risk and worse NYHA functional class was associated with prolonged hospital stay and mortality, both significant statistically.

Index Terms- Ejection fraction, Heart failure, Risk, outcomes

I. INTRODUCTION

HTHeart failure (HF) is an epidemic affecting 5.1 million American adults based on 2013 estimates, and this epidemic will grow 25% by 2030 as the United States population continues to age.[1] HF is one of the leading causes of death, approximately 30,000 deaths per year. Recent studies have indicated that more than half patients diagnosed with HF even though ejection fraction (EF) is normal or near normal.[2] Heart failure is a clinical diagnosis.[3] An ejection fraction (EF) of <50% in a patient with heart failure symptoms is termed heart

failure with reduced ejection fraction (HFREF), and an EF of \geq 50% in a patient with heart failure symptoms is termed heart failure with preserved EF (HFPEF). Heart failure can occur in patients in whom left ventricular systolic contractile function appears to be normal when measured by the ejection fraction. Since systolic function was presumed to be normal in these patients, this form of heart failure was thought to be due to diastolic dysfunction or abnormal filling.[4] Studies have demonstrated that HFPEF is as prevalent as HFREF.[5] It is important to note that the above terms are not mutually exclusive as nearly all patients with systolic dysfunction have some degree of concomitant diastolic dysfunction.[6]

There has been an apparently steady rise in the prevalence of HFPEF over the past decade.[7] Despite this, there has been considerable controversy with regards to the existence of the condition, its terminology, the characteristics of the condition and the diagnostic criteria for HFPEF. The confusion has arisen as some authors suggested that systolic function is normal in HFPEF patients,[8] while others questioned if the two entities exist as a continuum of heart failure or whether they are distinct entities.[9] There are differences in microscopic and neuroendocrine features which consequently lead to differences in left ventricular structure and echocardiographic characteristics between HFPEF and HFREF. These differences are attributed by underlying or contributing factors such as aging, hypertension, diabetes, female gender, dyslipidemia and obesity.[10] Diastolic dysfunction is categorized by Doppler echocardiographic findings into the following progression.[11] Mild (Grade I), defined as impaired relaxation without or with mild evidence of increased filling pressures respectively; Moderate (Grade II), defined as impaired relaxation associated with moderate elevation of filling pressures or pseudonormal filling, and Severe, defined as advanced reduction in compliance or reversible (Grade III) or fixed (Grade IV) restrictive filling.

The common risk factors associated with HFPEF i.e. hypertension, diabetes and coronary artery diseases are more prevalent in India.[12] The exact prevalence and incidence of HFPEF are not known, it indicates a need to carry out the study which gives us an idea regarding the prevalence, etiology, morbidity and mortality pattern of this study. So, we have carried out the study to obtain the clinical profile of the patients experiencing HFPEF along with etiology, pharmacological treatments and short-term outcomes.

II. METHODS

This was a tertiary care centre hospital based cross sectional observational study conducted at the cardiology unit of college of medical sciences Bharatpur, Nepal. Ethical approval of this study was obtained from the same hospital with written informed consent from each patients or relatives wherever necessary. We observed 200 newly admitted patients in coronary care unit and cardiology ward who fulfilled the Framingham’s criteria of heart failure [13]for clinical diagnosis and LV ejection fraction more than or equal to 50%. A Performa was used for collecting information at admission on demographics and co morbidities including history of hypertension, diabetes mellitus and others. Physical assessment was done on all patients, and patients classified according to NYHA classification. For the study, ECHO either done during in-patient stay or done in past two months was accepted for the study.

The investigator administered structured questionnaires to obtain information on outcomes at discharge, and on drug prescriptions related to heart failure at discharge. Patients were then given follow-up visit date. The investigator administered structured questionnaires and collected information on common symptoms of heart failure, NYHA classification, and QOL at one month. Data were analyzed using IBM-SPSS 20.0 (IBM Corporation, Armonk, NY, USA). The t- test and Chi-square test were used for statistical analysis. A p-value < 0.05 was considered statistically significant for all statistical tests unless otherwise stated.

III. RESULT

Out of 200 cases, 114(57%) were females and 86(43%) were males. The mean age of patient was 51.57(±16.81) years with range of 20 to 89 years. 2/3rd of cases were in the age group of 40 to 80 years. (Table 1)

Table 1: Clinico-epidemiological profile of patients (n=200)

Characteristic	Frequency	Percentage
Age (in years)		
<20	1	0.5
21-40	58	29
41-60	75	37.5
61-80	60	30
>80	6	3
Mean age ± SD (years)	51.57±16.81	
Gender		
Male	86	43
Female	114	57
Religion		
Brahmin	76	38
Chhetri	26	13
Newar	33	16.5
Magar	17	8.5
Tharu	12	6
Gurung	9	4.5
Others	27	13.5
Occupation		

Agriculture	78	39
Housewife	60	30
Businessmen	30	15
Service Holder	18	9
Ex- army	10	5
Student	4	2

The most common risk factors in our patients were Hypertension (78%) followed by obesity 55.5%, smoking (50%), dyslipidemia (48%), and Diabetes mellitus (48%), shown in figure 1. The most common presenting symptom was dyspnea (96%) followed by PND (55%), fatigue (51%) and cough (26%). Two patients presented with syncope as a presenting complaint. Figure 2.

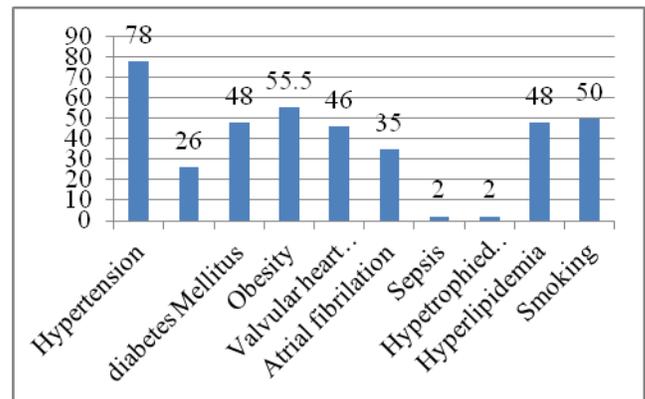


Figure1: Associated Risk factors in patients with heart failure(n=200)

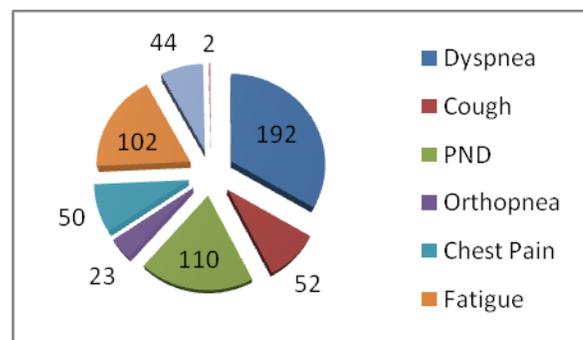


Figure 2: Presenting complains of patients with heart failure (n=200)

Majority (84%) of cases presented late in NYHA class of II and III. 12% presented with NYHA class IV. In this study 61 patients (30.5%), who presented with NYHA class I-II had hospitalization for less than 4 days and 9.5% with same NYHA class had hospitalization for more than 4 days, but the patients (53%), who presented with class III-IV were hospitalized for >4 days which was found to be statistically significant (P<0.001). Table 2.

Table 2. NYHA at presentation and duration of hospital stay in patients with heart failure (n=200)

Duration of stay in ward (days)	NYHA I-II	NYHA III-IV	P-VALUE
<4	61(30.5%)	2(1%)	0.127
4-7	4(2%)	68(34%)	<0.001
>7	15(7.5%)	38(19%)	

In this study increase in BMI (overweight, obesity class I and class II) was found in 55.5% which was statistically significant for development of left ventricular diastolic dysfunction (LVDD), P=<0.05. Similarly, HTN was classified

according to JNC-7, Pre-hypertension range of BP was found in 41.5% , stage 1 HTN in 24%, stage II HTN in 11%, 3% had isolated systolic HTN and 1% had isolated diastolic HTN. In our study 73% of patients were having abnormal ECG. The most common abnormality was LVH (31%) followed by sinus tachycardia (19.5%) and AF (17.5%).

Echocardiographic study showed mean LA 41.4(±8.4) mm, MR (Mitral Regurgitation) in 48%, TR (Tricuspid Regurgitation) was seen in 49.5%. Most of the patients had Grade I LVDD (84%) and none had Grade IV LVDD. LVMI (left ventricular mass index) was statistically significant with the Grade of LVDD (p<0.01), Similarly, E/A ratio, tissue doppler, at mitral annulus Septal E/e' & Lateral E/e', Deceleration time (msec) and IVRT (msec) were also statistically significant with the Grade of LVDD. Table 3.

Table 3: Correlation of echocardiography parameter and grade of LVDD (n=200)

	LVDD GRADE I	LVDD GRADE II	LVDD GRADE III	P-VALUE
LVMI	116(109-129)	128(106-139)	142(114-158)	<0.01
E/A Ratio	0.71(0.40-0.79)	1.0(0.8-1.2)	1.5(1.1-2.85)	<0.05
TDI,mitral annulus				
Septal E/e'	5.02(3.83-11.5)	10.4(9.2-11.9)	13.02(12.7-14.22)	<0.01
Lateral E/e'	4.11(4.31-7.22)	9.1(7.31-11.91)	12.01(11.23-15.20)	<0.05
Deceleration time (msec)	226(216-260)	190(174-220)	160(145-207)	<0.05
IVRT (msec)	91(73-106)	74(71-90)	66(55-58)	<0.05

In this study, 92.5% patients received diuretics (loop diuretics, potassium sparing diuretics or combination),65% received Antiplatelets, 53% were prescribed Statins. Similarly, Amlodipine (CCB), Angiotensin receptor blockers, Angiotensin converting enzymes inhibitors, Beta blockers, Nitrates and Digoxin in 39% , 22%, 17.5%, 14%, 9% and 8% respectively. Out of 200 patients, 4 patients died within 24 hours of hospitalization, all of them presented in NYHA class III-IV. 196 patients were discharged; only 117 patients were able to follow up either by telephone contact or during OPD visit or re-hospitalization within 30 days. 12.5% patients were re-hospitalized within 30days, among them 3 patients died and cause of death being refractory cardiogenic shock in 2 patients and the other died of sudden cardiac death.

IV. DISCUSSION

Heart failure is growing burden around the world. In the current study, 10.5% of the patient admitted in the cardiology unit had HFPEF which was 48.6% of the total heart failure cases over the study period. In epidemiological cohort studies done in USA in 2014 by [Charlotte Andersson](#) et al. (2014),[14] the prevalence of HFPEF approaches 10% for people >80 years of age; and incidence rates seem stable in the face of a growing prevalence. In a study done in Northeast China in 2012 by Liang Guo et al. [15] the prevalence of HFPEF was 4.8% in participants over 65 years old, which was consistent with the

result of a study conducted in central Italy that found a 4.9% HFPEF prevalence in 65–84 year-old individuals.[16] Hedberg et al. (2001),[17] reported that the prevalence of HFPEF in a population-based sample of 75-year-old participants was 6.8%. In the present study, majority of the patients, 2/3rd belong to age group 40-80 years. The mean age being 51.57±16.81 years, this is slightly lower than other studies.

The present study shows dyspnea (96%) and fatigue (51%) as commonest symptoms. 56% of the patients having dyspnea were in NYHA functional class III-IV. In a study done in India by Devasia et al. [18] Tachycardia was the commonest clinical sign (96%). Others were pedal edema (86%), raised JVP (63%) and pulmonary edema (46%). In present study commonest risk factor was HTN (78%), followed by obesity (overweight and class I & II obesity) 55.5%, smoking 50%, DM (48%), hyperlipidemia (48%) and AF(35%). In a study done in UK by Sosin et al.[19] obesity was found in, 36.3% with BMI>30 kg/m², 29.2% had diabetes,50.0% had hypertension, 5.7% had a history of myocardial infarction, and 1.9% had history of arrhythmia. In a study by Liang Guo et al,¹⁵ risk factors of HFPEF were hypertension 44.9%, dyslipidemia 38.4%, history of heart disease 16.6%, abdominal obesity 15.7%,diabetes in 11.3% and BMI>30 was seen 5.9% patients.

In a study done in 2014 by Burke et al. [20] in USA, risk factors of HFPEF were hypertension 77%, dyslipidemia 38.4%, history of heart disease (CAD) 48%, chronic kidney disease in 33%, diabetes in 33% and mean BMI of patients in study was 30±9. Similarly, a study done in patient with HFPEF in USA by

Lam et al.[21] Hypertension was present in 96% patients with mean SBP(132±23 mmHg) and mean DBP(67±14 mmHg).

In current study, Echcardiographic study showed mean LA 41.4(±8.4)mm, MR was seen in 48.5% and TR was seen in 49.5% cases. Most of the patients had Grade I LVDD 84%. PAH was seen in 57.5% and Regional wall motion abnormalities were seen in 11%. 10% patients had pericardial effusion among them 3 had moderate to large pericardial effusion and LA thrombus was seen in 1 patient. In a study done by Kaneko et al.[22] mean LA size was 4.13±1.0cm. In a study done by Yamamoto et al.[23] was 4.4±0.8cm, Similarly in a study done by Rossi et al.[24] mean LA size was 41±1.0cm. LA size is determined mainly by LV diastolic dysfunction. The relatively load-independency of a dilated LA provides an important advantage over Doppler parameters that are related to filling pressures. This is crucial as patients with HFPEF may have normal filling pressure at rest with disproportionate increase during effort. Thus, LA imaging may provide important clue for HFPEF diagnosis.[25]

In this study most of the patients 92.5%, were under diuretics which is the mainstay of treatment in heart failure. Other medication includes Antiplatelets, (65%), Statins (53%), CCB (39%), ARB (22%), ACEI (17.5%), B-blockers (14%), Nitrates (9%) and Digoxin (8%). In a study done in India by Devasia et al.¹⁸ drugs prescribed to the patients with HFPEF were Diuretics (92%), Antiplatelets (68%), Statins(63%), ACEI(58%), Amlodipine (34%), Nitrates(12%), B-blockers(8%) and Digoxin in 6% patients. There are several clinical trials in the HFPEF population targeting on clinical symptoms, exercise capacity, diastolic dysfunction, and quality of life (QoL). Although there are tested treatments improving these outcomes, no confirmed positive outcomes in regard to mortality were obtained from all pharmacological therapies including diuretics, beta-blockers, RAAS antagonists, digitalis, HMG-CoA-reductase inhibitors (statins), nondihydropyridine calcium channel blockers, and phosphodiesterase-5 inhibition (PDE-5 inhibition) so far.[25]

In this study QOL score at 30days was significantly associated with NYHA class on Admission (p<0.05), similarly QOL score at discharge was also significant with outcomes at 30days follow up (p=0.012), anemia at the time of admission as well as AF as risk of HFPEF were significant with outcomes at 30 days, (p=0.014) & (p<0.05). Out of 200 patients, 4 patients died within 24 hours of hospitalization, all of them presented in NYHA class III-IV at the time of hospitalization. A recent meta-analysis of 7688 patients with HFPEF followed for about 4 years found an overall mortality of 32% (about an 8% annual mortality rate).[27] In a study by Henkel et al.[28] annual mortality rates ranged from about 3.5 to 6% in 3 of the large randomized clinical trial to about 15% in the observational community-based Framingham Study.

V. LIMITATIONS

This was a hospital based study at a single site so the results may not be generalized to the community, however they could potentially be reference for further study at secondary and tertiary level hospitals. All the echocardiographic assessment parameters for left ventricular diastolic function could not be done in all the patients (eg.pulmonary S/D ratio, atrial reversal

velocity was done in selected cases whenever required). However, E/A ratio, reversal with valsalva (whenever indicated) and E/e' was done in all the studied patients. Proper and timely follow-up of the all patients could not be done.

VI. CONCLUSION

In conclusion, the incidence of heart failure with preserved ejection fraction (HFPEF) was more in female. Hypertension was the most common risk and worse NYHA functional class was associated with prolonged hospital stay and mortality. Although this study was done on single hospital and in a small population size, it revealed baseline information on heart failure with preserved ejection fraction which can be used as reference for further studies

ACKNOWLEDGEMENT

The authors express sincere gratitude to lab technician Mr. Indra Prasad Dumre and all the staff in the department of Cardiology. Also the authors are thankful to Mrs Ruchi Gupta for her contribution in preparing this manuscript. Authors also sincerely thank Mr. Naresh Manadhar for his contribution in the statistical analysis.

REFERENCES

- [1] Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics--2013 update: a report from the American Heart Association. *Circulation*. 2013; 127:e6–e245.
- [2] Maestre VG, Gallego J, Garcia M, Garcia de Burgos F, and Martín-Hidalgo A. Prediction Clinical Profile to Distinguish between Systolic and Diastolic Heart Failure in Hospitalized Patients. *European Journal of Internal Medicine*. 2009; 313-18.
- [3] McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. *NEJM*. 1971; 285:1441–6.
- [4] Chen CH, Nakayama M, Nevo E, Fetis BJ, Maughan WL, Kass DA. Coupled systolic-ventricular and vascular stiffening with age: implications for pressure regulation and cardiac reserve in the elderly. *J Am Coll Cardiol* 1998;32(5):1221-7.
- [5] Bursi F, Weston SA, Redfield MM, et al. Systolic and diastolic heart failure in the community. *JAMA*. 2006; 296:2209–16.
- [6] Redfield MM, Jacobsen SJ, Burnett JC Jr, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA*. 2003; 289:194–202.
- [7] Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *NEJM* 2006; 355(3):251-9.
- [8] Westermann D, Kasner M, Steendijk P, Spillmann F, Riad A, Weitmann K, et al. Role of left ventricular stiffness in heart failure with normal ejection fraction. *Circulation* 2008;117(16):2051-60.
- [9] De Keulenaer GW, Brutsaert DL. Diastolic heart failure: a separate disease or selection bias? *Prog Cardiovasc Dis* 2007;49(4):275-83.
- [10] Van Heerebeek L, Borbely A, Niessen HW, Bronzwaer JG, van d, V, StienenGJ, et al. Myocardial structure and function differ in systolic and diastolic heart failure. *Circulation* 2006; 113(16):1966-73.
- [11] Vasan RS, Levy D. Defining diastolic heart failure: A call for standardized diagnostic criteria. *Circulation* 2000; 101: 2118–2121.
- [12] Reddy, S., Bahl, A. and Talwar, K. Congestive Heart Failure in Indians: How Do We Improve Diagnosis & Management? *The Indian Journal of Medical Research*.2010; 132: 549.

- [13] McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. *NEJM*. 1971; 285(26):1441-6.
- [14] Charlotte Andersson, Ramachandran S Vasan, Epidemiology of heart failure with preserved ejection fraction. *Heart Fail Clin*. 2014; 10(3): 377–88.
- [15] Liang Guo,1 Xiaofan Guo,1 Ye Chang,1 Jun Yang,2 Limin Zhang,2 Tan Li, Prevalence and Risk Factors of Heart Failure with Preserved Ejection Fraction: A Population-Based Study in Northern China. *Int J Environ Res Public Health*.2016;13(8):377-388.
- [16] Mureddu, G.F, Agabiti, N, Rizzello et al. Prevalence of preclinical and clinical heart failure in the elderly. A population-based study in central Italy. *Eur. J. Heart Fail*. 2012, 14, 718–729
- [17] Hedberg P, Lonnberg I, Jonason T, Nilsson G, Pehrsson K, Ringqvist I. Left ventricular systolic dysfunction in 75-year-old men and women; A population-based study. *Eur. Heart J*. 2001, 22, 676–83.
- [18] Devasia T, Nandibandi SD, Bhat R., Kareem H, Thakka A. Clinical Profile and Treatment Management of Heart Failure with Preserved Systolic Function in Rural Setting of India. *International Journal of Clinical Medicine*. 5, 171-76.
- [19] Sosin MD, Bhatia GS, Davis RC, Lip GYH Heart Failure – the importance of ethnicity. *Eur J Heart Failure* 6: 831–43.
- [20] Burke MA, Katz DH, Beussink L, Selvaraj S, Gupta DK, Fox J, Chakrabarti S, Sauer AJ, Rich JD, Freed BH, Shah SJ. Prognostic importance of pathophysiologic markers in patients with heart failure and preserved ejection fraction. *Circ Heart Fail*. 2014; 7:288–99.
- [21] Lam CS, Roger VL, Rodeheffer RJ, Bursi F, Borlaug BA, Ommen SR, Kass DA, Redfield MM. Cardiac structure and ventricular-vascular function in persons with heart failure and preserved ejection fraction from Olmsted County, Minnesota. *Circulation*. 2007;115:1982–90.
- [22] Kaneko H. Role of cardiopulmonary dysfunction and left atrial remodeling in development of acute decompensated heart failure in chronic heart failure with preserved left ventricular ejection fraction. *J Cardiol*. 2012; 59:359–65.
- [23] Yamamoto K, Origasa H, Suzuki Y, Takahashi T, Shinozaki T, Watanabe T. DHF Investigators. Relation of risk factors with response to carvedilol in heart failure with preserved ejection fraction - a report from the Japanese Diastolic Heart Failure Study (J-DHF). *J Cardiol*. 2014;63:424–31.
- [24] Rossi A, Ciccoira M, Florea VG, Golia G, Florea ND, Khan AA. Chronic heart failure with preserved left ventricular ejection fraction: diagnostic and prognostic value of left atrial size. *Int J Cardiol*. 2006;110:386–92.
- [25] Douglas PS. The left atrium: a biomarker of chronic diastolic dysfunction and cardiovascular disease risk. *J Am Coll Cardiol*. 2003; 42:1206–1207.
- [26] Yip GWK, Wang M, Wang T et al. “The Hong Kong diastolic heart failure study: a randomised controlled trial of diuretics, irbesartan and ramipril on quality of life, exercise capacity, left ventricular global and regional function in heart failure with a normal ejection fraction,” *Heart*. 2008; 94 (5) 573–80.
- [27] Ahmed A, Rich MW, Fleg JL et al. Effects of digoxin on morbidity and mortality in diastolic heart failure: the ancillary digitalis investigation group trial. *Circulation*. 2006;114:397–403.
- [28] Henkel DM, Redfield MM, Weston SA, Gerber Y, Roger VL. Death in heart failure: a community perspective. *Circ Heart Fail*. 2008; 1:91–97.

AUTHORS

First Author: Dr. Rajesh Kumar Panjiyar,
MD Internal medicine, DM Cardiology
Consultant Physician and Cardiologist, College of Medical
Sciences, Bharatpur, Nepal
Email: panjiyar.rajesh@gmail.com

Second Author: Dr. Ram Sundar Twayana,
MD Internal Medicine
Specialty Registrar, Respiratory Medicine,
Sandwell and West Birmingham Hospitals, NHS Trust,
Birmingham, United Kingdom
Email: ram.twayana@nhs.net

Third Author: Dr. Shankar Laudari
MD Internal Medicine, DM Cardiology
Lecturer and Cardiologist, College of Medical Sciences,
Bharatpur, Nepal
Email: lshankar2@hotmail.com

Fourth Author: Dr. Sachin Dhungel
MD Internal Medicine, DM Cardiology
Lecturer and Cardiologist, College of Medical Sciences,
Bharatpur, Nepal
Email: sachindhungel@hotmail.com

Fifth Author: Dr. Madhu Gupta
MD Internal Medicine, DM Resident
College of Medical Sciences, Bharatpur, Nepal
Email: madhugupta.md@gmail.com

Sixth Author: Dr. Laxman Dubey
MD Internal Medicine, DM Cardiology
Associate Professor, College of Medical Sciences, Bharatpur,
Nepal
Email: dubeylax@yahoo.com

Seventh Author: Dr. Gagnapatnam Subramanyam,
DM Cardiology
Professor and Head of Department, College of Medical Sciences,
Bharatpur, Nepal
Email: info@cmsnepal.edu.np

Corresponding Author: Dr. Ram Sundar Twayana, MD Internal
Medicine
Specialty Registrar, Respiratory Medicine,
Sandwell and West Birmingham Hospitals, NHS Trust,
Birmingham, United Kingdom
Email: ram.twayana@nhs.net
Contact: +44 07533651659, +44 0121 553 1831