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ASSOCIATION OF DOOR TO DIURETIC TIME ON MORTALITY AND MORBIDITY IN ACUTE HEART FAILURE

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ABSTRACT

This study was prospective, observational study of patients hospitalized for acute heart failure (AHF). All patients were followed up for six months after the index hospitalization. Early group (n = 137) received IV diuretics within 90 minutes while as Delayed group (n = 293) received IV diuretics after 90 minutes. Demographic parameters like age, gender and comorbid illness was compared in patients in Early Group and Delayed Group and the association was found to be statistically insignificant (p >0.05). Insignificant statistical difference was observed when smoking status was compared between two study groups. There were 21.9% smokers in Early Group compared to 17.4% smokers in Delayed Group. On echocardiography, heart failure with preserved ejection fraction (HFpEF) was observed in 48.1% patients, heart failure with reduced ejection fraction (HFrEF) was seen in 39.1% patients and 12.8% patients had heart failure with midrange ejection fraction (HFmrEF). In-hospital mortality was higher in Delayed Group (12.3%) compared to Early Group (5.1%) with significant statistical difference ($p < 0.05$). Mean length of hospitalization was shorter in Early Group (14.7 days) compared to 17.3 days in Delayed Group ($P < 0.05$). Readmission at 1 month in two study groups was found to be statistically insignificant ($p>0.05$) with 13.9% in Early Group compared to 16.4% in Delayed Group. Readmission at 6 month was again higher in Delayed Group 12.3% versus 9.5% in Early Group with an insignificant statistical association ($p > 0.05$). At one month significantly higher mortality was observed in Delayed Group (14.3%) compared to 7.3% in Early Group ($p<0.05$). At 6 month, there was higher mortality in Delayed Group (22.9%) compared to 13.1% in Early Group with a statistically significant association between ($p <0.05$).

Keywords: acute heart failure, reduced ejection fraction, preserved ejection fraction, readmission, mortality

INTRODUCTION

Heart failure (HF) is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood leading to cardinal manifestations of dyspnoea, fatigue and fluid retention[1]. Prevalence of heart failure is 3.9 cases/1000. Prevalence of heart failure increased considerably with age – in those aged under 65 years the prevalence rate was 0.6 cases/1000 compared to 28 cases/ 1000 in those aged over 65 years[2].

The main reason for an acute heart failure hospitalization is signs or symptoms of congestion for which the first-choice treatment is administration of loop diuretics. These aim to establish a negative fluid balance, and thus alleviate signs and symptoms associated with fluid overload. Diuretics have been used in acute heart failure for many years, even though large, randomized studies are lacking. Several small studies and case reports after the introduction of loop diuretics showed that the absorption of loop diuretics in heart failure patients was delayed[3-6]. Additionally, the dose response curve is thought to be shifted downwards and to the right, meaning that the maximal response that can be obtained is diminished[7]. Based on these findings heart failure patients are considered relatively diuretic resistant, and a poor response to diuretics frequently occurs during hospitalization for heart failure[8,9].

The main aim of AHF therapy is to achieve decongestion, which is predominantly realized by administration of diuretics. Failure to respond adequately to diuretic therapy, termed diuretic resistance, is a complicating factor that is associated with poor outcome and high rehospitalization rates[9,10,11]. Two slightly different, simple, quantitative measures to assess diuretic response combining either urine output or weight loss and diuretic dose have been recently proposed[10,11,12]. Using these definitions, poor diuretic response was associated with more advanced heart failure, renal impairment, diabetes, atherosclerotic disease and in-hospital worsening heart failure. Importantly, a poor diuretic response also strongly predicted mortality and heart failure rehospitalization. Early identification of diuretic resistant patients is therefore important and might lead to adaptation of treatment strategies.

AIMS AND OBJECTIVES

- To study the impact of door-to-diuretic (D2D) time on mortality in patients with acute heart failure (AHF).
- To study the impact of door-to-diuretic (D2D) time on length of hospital stay and readmission rate in patients with acute heart failure (AHF).

MATERIALS AND METHODS

This study was prospective, observational study of patients hospitalized for acute heart failure (AHF) in Department of Medicine SMHS Hospital, Srinagar. Patients for the study were selected based on eligibility criteria. All patients were followed up for six months after the index hospitalization. The study was carried out over a period of two years in the Postgraduate Department of Medicine at Government Medical College, Srinagar from December 2020 to December 2022, after approval from Institutional Ethical Committee. Written informed consent in the local commonly used language was obtained from all the participants before their inclusion in the study.

Inclusion Criteria

- Age ≥ 18 years.
- Signs or symptoms of heart failure (HF) and lung congestion.
- Objective findings of left ventricular systolic and diastolic dysfunction.

Exclusion Criteria

- Patients who received the first dose of furosemide 24 h after ED arrival.
- Patients who are undergoing long-term dialysis therapy before hospital admission.
- Patients who received oral furosemide in ED.

Statistical Methods: The recorded data was compiled and entered in a spreadsheet (Microsoft Excel) and then exported to data editor of SPSS Version 20.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as Mean ± SD and categorical variables were summarized as frequencies and percentages. Graphically the data was presented by bar and pie diagrams. Student's independent t-test or Mann-Whitney U-test, whichever feasible, was employed for comparing continuous variables. Chi-square test or Fisher's exact test, whichever appropriate, was applied for comparing categorical variables. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The mean age of the study patients in early group was 61.9±15.82 years compared to 62.7±17.15 years in delayed group. Early group (n = 137) received IV diuretics within 90 minutes while as Delayed group (n = 293) received IV diuretics after 90 minutes. Age was statistically insignificant between Early and Delayed Groups (p 0.645). There was male dominance in both the study groups with 84 (61.3%) males and 53 (38.7%) females in Early Group compared to 175 (59.7%) males and 118 (40.3%) females in Delayed Group. The difference was found to be statistically insignificant with a p value of 0.579. There were 30 (21.9%) smokers in Early Group compared to 51 (17.4%) in Delayed Group. When patients in two study groups were compared based on smoking status the difference was found to be statistically insignificant (p 0.267).

Hypertension was the commonest comorbid illness observed in 97 (70.8%) patients in Early Group and 198 (67.6%) patients in Delayed Group followed by diabetes mellitus in 51 (37.2%) patients and 103 (35.2%) patients in Early and Delayed Groups, respectively. Ischemic heart disease was seen in 39 (28.5%) patients in Early Group compared to 71 (24.2%) patients in Delayed Group, valvular heart disease was observed in 16 (11.7%) patients in Early Group compared to 42 (14.3%) patients in Delayed Group, atrial fibrillation was observed in 31 (22.6%) and 84 (28.7%) patients in Early and Delayed Group, respectively while 13 (9.5%) patients in Early Group and 37 (12.6%) patients in Delayed Group had COPD. Statistically insignificant difference was observed when comorbid illnesses were compared between two study groups (p>0.05).

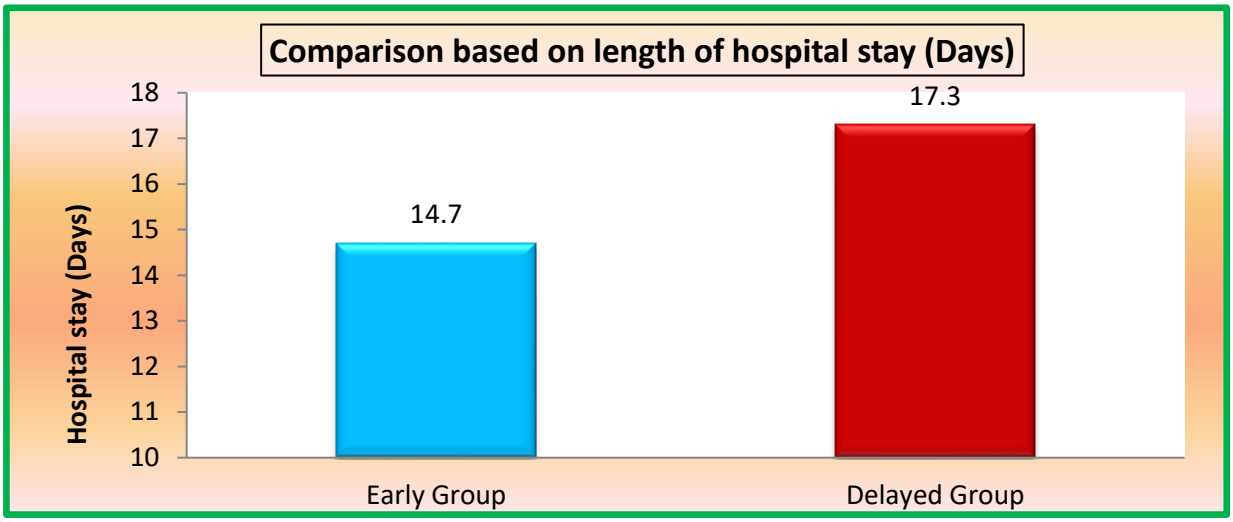
On echocardiography, heart failure with preserved ejection fraction (HFpEF) was observed in 207 (48.1%) patients, heart failure with reduced ejection fraction (HFrEF) was seen in 168 (39.1%) patients, 55 (12.8%) patients had heart failure with midrange ejection fraction (HFmrEF). There was 5.1% (n=7) in-hospital mortality in early group compared to 12.3% (n=36) in delayed group. In-hospital mortality was highly significant in Delayed Group compared to Early Group with a p value of 0.021. (Table 1)

Table 1: In-hospital mortality in two groups

In-hospital mortality	Early Group		Delayed Group		P-value
	No.	%age	No.	%age	
Yes	7	5.1	36	12.3	0.021*
No	130	94.9	257	87.7	
Total	137	100	293	100	

***Statistically Significant Difference (P-value <0.05)**

Mean hospital stay in 137 patients in Early Group was 14.7±7.89 days with a 95% CI of 10.7-18.3 compared to mean hospital days of 17.3±8.54 days with a 95% CI of 13.4-22.8 in 293 patients in Delayed Group. The length of hospital stay was observed to be statistically significant (p 0.003) between the two study groups (Table 1).



Readmission rate at 1 month was 13.9% (n=19) in Early Group compared to 16.4% (n=48) in Delayed Group. The relation observed between patients in Early Group and Delayed Group was found to be statistically insignificant (p 0.503) (Table 2).

Table 8: Readmission rate at 1 month in two groups

Readmission	Early Group		Delayed Group		P-value
	No.	%age	No.	%age	
Yes	19	13.9	48	16.4	0.503
No	118	86.1	245	83.6	
Total	137	100	293	100	

Mortality at one month was higher in Delayed Group (14.3%, n=42) compared to (7.3%, n=10) Early Group. The difference observed was statistically significant with a p value of 0.037. (Table 3)

Table 3: Mortality at one month in two groups

Mortality	Early Group		Delayed Group		P-value
	No.	%age	No.	%age	
Yes	10	7.3	42	14.3	0.037*
No	127	92.7	251	85.7	
Total	137	100	293	100	

***Statistically Significant Difference (P-value <0.05)**

There were 9.5% (n=13) patients in Early Group who were readmitted at 6 months compared to 12.3% (n=36) patients in Delayed Group. The difference observed was statistically insignificant (p 0.395) (Table 4).

Table 10: Readmission rate at 6 months in two groups

Readmission	Early Group		Delayed Group		P-value
	No.	%age	No.	%age	
Yes	13	9.5	36	12.3	0.395
No	124	90.5	257	87.7	
Total	137	100	293	100	

At 6 months, there was higher mortality in Delayed Group (22.9%, n=67) compared to 13.1% (n=18) in Early Group with a statistically significant association between mortality at 6 months in Early and Delayed Group with a p value of 0.018.

Table 11: Mortality at 6 months in two groups					
Mortality	**Early Group**		**Delayed Group**		**P-value**
	No.	**%age**	**No.**	**%age**	
Yes	18	13.1	67	22.9	0.018*
No	119	86.9	226	77.1	
Total	137	100	293	100	

***Statistically Significant Difference (P-value <0.05)**

DISCUSSION

Heart failure (HF) is a clinical syndrome, which is becoming a major public health problem in recent decades, due to its increasing prevalence, especially in the developed countries. HF is a major cause of morbidity and mortality worldwide. Globally, >26 million people are affected by HF. In primary care, the overall 5-year survival following the diagnosis of HF is ~50%. For patients with severe HF, the 1-year mortality may be as high as 40%. Most of these patients die of cardiovascular causes, most commonly progressive HF or sudden cardiac death. HF is one of the most frequent causes of hospitalizations and multiple hospitalizations. Diuretics are the mainstay for the treatment of AHF[13]. Early and rapid treatment in the Emergency Department is an important step in management[14]. Several studies have substantiated the positive effect of early treatment on the prognosis of patients with AHF, and the delay was associated with a significant increase in the risk of in-hospital mortality (IHM)[15].

The present study was done at SMHS hospital, GMC Srinagar over a period of two years. A total of 430 patients were included in the study. The purpose of this study was to study the effect of door-to-diuretic time on clinical outcomes in patients with acute heart failure. In our study, mean age of the study patients in early group was 61.9±15.82 years compared to 62.7±17.15 years in delayed group. Most common age group affected was 61-70 years in Early Group (57/137) and Delayed Group (125/293) followed by 51-60 years in 38/137 patients and 83/293 patients in Early and Delayed Groups, respectively. Least number of patients in Early Group 5/137 and Delayed Group 7/293 belonged to the age group of <40 years. Age was statistically insignificant between Early and Delayed Groups (p 0.645). There was male dominance in both the study groups with 84 (61.3%) males and 53 (38.7%) females in Early Group compared to 175 (59.7%) males and 118 (40.3%) females in Delayed Group. The difference was found to be statistically insignificant with a p value of 0.579. Hypertension was the commonest comorbid illness observed in 97 (70.8%) patients in Early Group and 198 (67.6%) patients in Delayed Group followed by diabetes mellitus in 51 (37.2%) patients and 103 (35.2%) patients in Early and Delayed Groups, respectively. Ischemic heart disease was seen in 39 (28.5%) patients in Early Group compared to 71 (24.2%) patients in Delayed Group, valvular heart disease was observed in 16 (11.7%) and 42 (14.3%) patients in Early and Delayed Groups, respectively. Atrial fibrillation was observed in 31 (22.6%) and 84 (28.7%) patients in Early and Delayed Group, respectively while 13 (9.5%) patients in Early Group and 37 (12.6%) patients in Delayed Group had COPD. Statistically insignificant difference was observed when comorbid illnesses were compared between two study groups (p > 0.05).

In our study, there were 30 (21.9%) smokers in Early Group compared to 51 (17.4%) patients in Delayed Group. When patients in two study groups were compared based on smoking status the difference was found to be statistically insignificant (p 0.267). In our study, on echocardiography, heart failure with preserved ejection fraction (HFpEF) was observed in 207 (48.1%) patients, heart failure with reduced ejection fraction (HFrEF) was seen in 168 (39.1%) patients, 55 (12.8%) patients had heart failure with midrange ejection fraction (HFmrEF). Park JJ et al., (2018)[16] did a study in heart failure with preserved ejection fraction (HFpEF) was observed in 62.7% patients in Early Group compared 58.7% in Delayed Group, heart failure with reduced ejection fraction (HFrEF) was seen in 14.7% patients in Early Group compared to 14.2% in Delayed Group while 22.5% patients in Early Group and compared to 27.1% patients in Delayed Group. The difference observed was statistically insignificant with a p value of 0.087. In the present study, there was 5.1% (n=7) in-hospital mortality in early group compared to 12.3% (n=36) in delayed group. In-hospital

mortality was higher in Delayed Group compared to Early Groups with a p value of 0.021. This is consistent with study done by Iqbal AM et al (2021)[17] where they found that patients in Delayed Group were 1.43 times more likely to have died compared to patients in Early Group.
Matsue Y et al., (2017)[15] prospectively evaluated the association between time-to-diuretic treatment and clinical outcome. In their study, in-hospital mortality was significantly lower in the early treatment group (2.3% vs. 6.0% in the non-early treatment group; p=0.002). Viriyanukulvong KV et al., (2021)[18] evaluated in-hospital outcomes after receiving early versus delayed intravenous furosemide injection among AHF patients. Among 820 enrolled AHF patients, the rate of total in-hospital death was 3.1% in Early Treatment Group vs. 6% in Delayed Treatment Group.
In present study, mean hospital stay of 137 patients in Early Group was 14.7+7.89 days with a 95% CI of 10.7-18.3 compared to mean hospital days of 17.3+8.54 days with a 95% CI of 13.4-22.8 in 293 patients in Delayed Group. The difference in length of hospital stay was observed to be statistically significant (p 0.003) between Early and Delayed Group. This is in accordance with study done by Iqbal AM et al., (2021)[17]. Where they found in early group average LOS was noted to be associated with shorter hospitalization (average of 1.423 days less as compared to group 2 (delayed group) patients (confidence interval (CI) =1.02-1.82; $p<0.05$). In our study, readmission rate at 1 month was 13.9% (n=19) in Early Group compared to 16.4% (n=48) in Delayed Group. The relation observed between patients in Early Group and Delayed Group was found to be statistically insignificant (p 0.503). In present study Mortality at one month was higher in Delayed Group (14.3%, n=42) compared to Early Group (7.3%, n=10). The difference observed was statistically significant with a p value of 0.037. Matsue Y et al., (2017)[15] reported that early treatment was associated with lower 30-day mortality compared to delayed group with p value statistically insignificant.
In our study, there were 9.5% (n=13) patients in Early Group who were readmitted at 6 months compared to 12.3% (n=36) patients in Delayed Group, this was statistically insignificant with p value of 0.395. In present study, at 6 month there was higher mortality in Delayed Group (22.9%, n=67) compared to 13.1% (n=18) in Early Group with a statistically significant association (p value=0.018) this is consistent with study done by. Mir J et al., (2020)[19] where they find the association between door to diuretic time on the clinical outcome for the patients who presented to Emergency department. Outcomes associated with diuretic timing showed no difference for length of stay or readmission rate but there was a significant difference in mortality with 1.1% in those given diuretics at 120 minutes or less compared to 3.5% patients were given diuretics at greater than 120 minutes (p=0.041). They concluded that door to diuretic time greater than 120 minutes was associated with 3.4-fold increased risk of mortality.

CONCLUSION

We conclude door to diuretic time greater than 90 minutes is associated with increased risk of mortality. Time lavished before treatment initiation is an important modifiable risk factor in heart failure. Further research is required to establish cut points for admission, serial measurement, change following admission and discharge levels to assist clinical decision-making.

BIBLIOGRAPHY

1. American College of Cardiology https://www.acc.org/education-and-meetings/ products-and-resources/features/global-cv-institute/heart-failure-guidelines
2. McMurray JJ and Stewart S. Epidemiology, aetiology, and prognosis of heart failure. Heart (British Cardiac Society), 2000;83(5):596–602.
3. Brater DC, Day B, Burdette A, Anderson S. Bumetanide and furosemide in heart failure. Kidney International, 1984;26(2):183–189.
4. Cook JA, Smith DE, Cornish LA, Tankanow RM, Nicklas JM, Hyneck ML. Kinetics, dynamics, and bioavailability of bumetanide in healthy subjects and patients with congestive heart failure. Clin Pharm Therap, 1988;44(5):487–500.

5. Brater DC, Seiwell R, Anderson S, Burdette A, Dehmer GJ, Chennavasin P. Absorption and disposition of furosemide in congestive heart failure. Kidney International, 1982; 22(2): 171–176.
6. Odlind BO, Beermann B. Diuretic resistance: reduced bioavailability and effect of oral frusemide. BMJ, 1980;280(6231):1577. https://doi.org/10.1136/bmj.280.6231.1577.
7. Brater DC. Pharmacokinetics of loop diuretics in congestive heart failure. British Heart Journal, 1994;72(2 Suppl):S40–S43.
8. Ellison DH. Diuretic therapy and resistance in congestive heart failure. Cardiology, 2001;96(3-4):132–143.
9. Neuberg GW, Miller AB, O'Connor CM, Belkin RN, Carson PE, Cropp AB et al. Diuretic resistance predicts mortality in patients with advanced heart failure. American Heart Journal, 2002;144(1):31–38.
10. Valente MA, Voors AA, Damman K, Van Veldhuisen DJ, Massie BM, O'Connor CM et al. Diuretic response in acute heart failure: clinical characteristics and prognostic significance. Eur Heart J. 2014 May 14;35(19):1284-93.
11. Voors AA, Davison BA, Teerlink JR, Felker GM, Cotter G, Filippatos G et al. Diuretic response in patients with acute decompensated heart failure: characteristics and clinical outcome--an analysis from RELAX-AHF. Eur J Heart Fail. 2014 Nov; 16(11): 1230-40.
12. Testani JM, Brisco MA, Turner JM, Spatz ES, Bellumkonda L, Parikh CR, Tang WH. Loop diuretic efficiency: a metric of diuretic responsiveness with prognostic importance in acute decompensated heart failure. Circ Heart Fail. 2014 Mar 1; 7(2): 261-70.
13. Somberg JC, Molnar J. The management of acute heart failure and diuretic therapy. American Journal of Therapeutics, 2009;16(1):93–97.
14. Cowie MR, Anker SD, Cleland JGF, Felker GM, Filippatos G, Jaarsma T et al. Improving care for patients with acute heart failure: before, during and after hospitalization. ESC Heart Fail. 2014 Dec;1(2):110-145.
15. Matsue Y, Damman K, Voors AA, Kagiyama N, Yamaguchi T, Kuroda S et al. Time-to-Furosemide Treatment and Mortality in Patients Hospitalized With Acute Heart Failure. J Am Coll Cardiol. 2017 Jun 27;69(25):3042-3051.
16. Park JJ, Kim SH, Oh IY, Choi DJ, Park HA, Cho HJ et al. The Effect of Door-to-Diuretic Time on Clinical Outcomes in Patients With Acute Heart Failure. JACC Heart Fail. 2018 Apr;6(4):286-294.
17. Iqbal AM, Mohammed SK, Zubair N, Mubarik A, Ahmed A, Jamal SF et al. The impact of door to diuretic time in acute heart failure on hospital length of stay and in-patient mortality. Cureus. 2021 Jan 16;13(1):e12742. doi: 10.7759/cureus.12742.
18. Viriyanukulvong KV, Han-Gla AH, Phannajit JP, Ariyachaipanich AA. Door-to-Furosemide time effects on in-hospital mortality and length of stay in acute heart failure patients. European Heart Journal. 2021 Oct 1;42(Supplement_1):ehab724-0897.
19. Mir J, Mumtaz S, Alan M, Bell T, Malik A. Effect of door to diuretic time in acute heart failure. Journal of Cardiac Failure. 2020;26(10):S47. DOI:10.1016/j.cardfail.2020.09.138.