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AGGRESSIVE DIURESIS AND SEVERITY-ADJUSTED LENGTH OF HOSPITAL STAY IN ACUTE CONGESTIVE HEART FAILURE PATIENTS

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AGGRESSIVE DIURESIS AND SEVERITY-ADJUSTED LENGTH OF HOSPITAL
STAY IN ACUTE CONGESTIVE HEART FAILURE PATIENTS

THESIS

A thesis submitted in partial fulfillment of the requirements for the degree of
Master of Science in the College of Public Health at the
University of Kentucky

By

Muhammad Umer Butt M.D.

Lexington, Kentucky

Director: Dr. David Mannino, Professor of Medicine

Lexington, Kentucky

2018

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ABSTRACT OF THESIS:

AGGRESSIVE DIURESIS AND SEVERITY-ADJUSTED LENGTH OF HOSPITAL
STAY IN ACUTE CONGESTIVE HEART FAILURE PATIENTS

To see if aggressive diuresis in first twenty four hours is associated with a comparable number of total days in the hospital as compared to non-aggressive diuresis. In this retrospective cohort study, we compared the length of hospital stay of consecutive patients admitted in one year based on their diuresis during the first twenty-four hours of hospitalization: aggressive diuresis (group 1) i.e. $>2400\text{mL}$ versus non-aggressive diuresis (group 2) i.e. $\leq 2400\text{mL}$ urine output. Patients were excluded if in cardiogenic shock, had creatinine level above 3 mg/dL on admission, or on dialysis. A total of 194 patients were enrolled (29 in group 1 and 165 in group 2 respectively). The Kaplan-Meier estimate of the median cumulative proportion of patients still hospitalized for the group 1 was 4 days and in group 2 was 5 days (log-rank test; $P=0.67$). In univariate analysis, Cox PH regression showed unadjusted hazard rate of discharge from hospital was slightly higher in group 1 than group 2 but was statistically non-significant ($\text{HR}=1.08$; $P=0.70$). In multivariate Cox model analysis, creatinine at the time of admission when greater than 1.6mg/dL ($P=0.75$), LVEF ($P=0.14$), total twenty-four hours dose of intravenous Furosemide given ($P=0.98$) and interaction between Furosemide dose and Creatinine level ($P=0.79$) were not significant predictor of hospital discharge. Adjusted hazard rate for discharge from hospital was 12% higher in group 1 than group 2 but still statistically non-significant ($\text{HR}=1.12$; $P=0.60$). Since the length of hospital stay is similar between two groups, we suggest the goal of diuresis to be less than 2400mL in first twenty four hours to prevent excessive dehydration.

Keywords: Aggressive Diuresis, Furosemide, length of hospital stay, Chronic Kidney Disease

Muhammad Umer Butt M.D.

Signature

April 30, 2018

Date

AGGRESSIVE DIURESIS AND SEVERITY-ADJUSTED LENGTH OF
HOSPITAL STAY IN ACUTE CONGESTIVE HEART FAILURE
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1.1 BACKGROUND:

Heart failure is a clinical syndrome associated with reduced effective blood pumping capacity of the heart. Congestive Heart Failure(CHF) is a global pandemic affecting at least 26 million people worldwide and 6.5 million people in the US with age ≥ 20 years.¹ Increase in incidence and prevalence of CHF is not due to the failure in treatment but an increased survival in the aging population who suffer from Acute Coronary Syndrome and related diseases of the heart. Heart failure is the most common diagnosis related reason for hospitalization in ≥ 65 -year-old patients. The total direct cost of the CHF patients has been estimated to be around \$ 20 to \$ 40 billion annually with the mean estimated cost of each hospitalization of \$14,631. Economic burden of CHF is further compounded by about 25% readmission rate within 30 days.² National average length of hospital stay is around 6 to 8 days.^{3,4} Medicare reimbursement for CHF patient is linked to the length of hospital stay and quality measures.⁴ There are situations during uncomplicated hospital admission, where expenses borne by the hospital exceed the reimbursement from insurance companies incurring undesirable financial penalties. There is an inherent desire to shorten the length of hospital stay without increasing the morbidity, mortality, and hospital re-admission rate.

Acute CHF is associated with on average up to 15 to 20 liters of extra fluid in the body. There are multidimensional approaches in the treatment of CHF depending on the etiology, type, and severity of CHF, but diuretics have been the time-tested cornerstone of every treatment. Loop diuretics are the effective first line diuretic therapy.⁵ Relieving congestion is the primary goal, but it is not always free from adverse effects of hypotension, worsening of renal function, electrolytes abnormality, and arrhythmias.

There are no clinical trials that define the ideal diuretic dose, thus, dosing is largely based on iterative increases with observation of patients for urine output, subjective assessment of patient fluid overload status, ejection fraction, home dose of diuretics, blood pressure at presentation, concurrent use of other medications, comorbidities, and renal function. Practically speaking, after hospital admission with acute congestive heart failure, the patient is empirically given the first dose of diuretic in the emergency room. As the patient is reassessed and given a subsequent dose of a loop diuretic, the relief of symptoms and ultimately the length of hospital stay depend partly on weight change or indirectly urine output. A common observation is that a high dose of diuretic does not necessarily translate into greater urine output in many situations, as numerous variables confound this relationship i.e. tolerance to diuretics, decrease GI absorption, hyperchloremia, and the severity of CHF and renal dysfunction at baseline or during the hospital stay. The goal of therapy is to maximize the urine output, but too much diuresis in a short time can lead to adverse effects. All treatments are directed towards starting certain adequate dose loop diuretic, but there is no magic number. The dose of diuretic given is merely one of the factors that can affect subjective relief of symptoms and length of hospital stay, but final urine output achieved by a diuretic dose has more intuitive and deterministic role practically.⁶ It is the eventual objective outcome depicting the effect of a diuretic. Thus, adequate diuresis achieved initially irrespective of starting dose of diuretic used can be assumed to have a direct role in relieving fluid overload symptoms. The total dose of diuretic given in first twenty-four hours which is highly variable likely helps to choose the subsequent tolerable dose, but it is only one of the factors determining the amount of urine if comorbidities or adverse effect of diuresis do not complicate the

course of the hospital. The DOSE trial addressed the primary question if symptomatic improvement, worsening of renal function is related to low vs. high dose of loop diuretic given as continuous vs. bolus dose protocols.⁷ This study did not find any difference in primary endpoint as well as its prespecified secondary endpoint of any difference in the length of hospital stay between four groups. But the study was not powered to detect the difference in the length of hospital stay, more so ever there was no comparison of urine output between the groups. However, two observational studies, first by Howard and Dunn and later by Li and Hong found that aggressive diuretic therapy to achieve greater than 100mL/hour ($\geq 2400\text{mL}/24$) of urine leads to a shorter length of hospital stay.^{3,8} Therefore, there are conflicting results between the dose of diuretic, subsequently urine output and length of hospital stay. Numerous studies have addressed the relationship between the dose of diuretic and length of hospital stay, but here we rather propose to examine the more direct relationship between the amount of diuresis in first twenty-four hours irrespective of dose of a loop diuretic and disease severity-adjusted length of hospital stay.

1.2 OBJECTIVES:

PRIMARY OBJECTIVE

The dose of diuretic is directly related to the urine output if there are no untoward effects and other disease severity associated predictors are accounted for. The higher the urine output, the earlier the relief of symptoms and the shorter the length of hospital stay. Since fluid overload is the primary pathological mechanism in acute congestive heart

failure patients, theoretically, diuresis driven by urine output itself achievable by any dose of diuretic would be better able to determine the decongestion and length of hospital stay. Patients will be divided into aggressive diuretic therapy group and non-aggressive diuresis group by the criterion used by Howard and Dunn.³ Expectantly it will be of interest to see if higher urine output leads to a shorter hospital stay.

Hypothesis:

Patients who had aggressive diuresis in first twenty-four hours (urine output \geq 2400mL/24 hour) will have a different a length of hospital stay than patients who had less-aggressive diuresis. (urine output $<$ 2400mL/24hour) irrespective of the dose of loop diuretics.

DESCRIPTIVE OBJECTIVE:

1 Study the association of dose of diuretics in first twenty-four-hour urine output using univariate and multivariate analysis, defining the predictors of association.

2 Study the risk of developing adverse effects as arrhythmia, worsening of renal function, electrolyte abnormality, and death in aggressive and non-aggressive diuretic therapy group.

STUDY DESIGN AND METHODS:

2.1 STUDY DESIGN AND POPULATION:

To examine the association between the amount of urine output in first twenty-four hours in acute CHF patients and the total length of hospital stay we propose to conduct a retrospective cohort study utilizing data from Mercy Hospital of South Buffalo,

affiliated with the State University of Buffalo. This hospital has a capacity of 450 beds and serves a population of approximately 1,500,000. Acute medical care of CHF is provided predominantly by residents, fellows, internists, and cardiologists. Patients admitted to the acute general medical wards and Cardiac Care Units either as a first diagnosis or an exacerbation of pre-existing HF between 2014 and 2015 will be prospectively identified by using International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] diagnosis code. Detailed data will be recorded retrospectively from the hospital records of each index hospital admission. The study will not include any vulnerable population.

2.2 INCLUSION CRITERIA:

Patients included will be 18- 80 years old who presented with new onset or chronic CHF diagnosed by elevated filling pressures, indicated by one symptom *and* one physical sign regardless of ejection fraction.

- *Symptoms:* Dyspnea at rest, in the supine position, or immediately upon routine activity within one room; abdominal discomfort, severe anorexia, or nausea without apparent cause other than hepatosplanchnic congestion.
- *Signs:* Jugular venous pressure elevation >10 cm above the right atrium; hepatomegaly, ascites, or edema in the absence of other apparent causes; rales greater than 1/3 lung fields and/ or pleural effusion.
- *Imaging documentation:* of congestive heart failure including pulmonary vascular congestion in chest x-ray will supplement the signs and symptoms.

2.3 EXCLUSION CRITERIA:

- Patients will be excluded if creatinine level greater than 3 mg/dl on admission or if the patient is on dialysis.
- Patient will also be excluded if in cardiogenic shock defined as systolic blood pressure below 90 mm Hg and requiring the use of inotropic medication or mechanical support.
- Patient will be excluded if they had any acute concurrent medical illness as Acute Coronary Syndrome, COPD or Asthma Exacerbation.

2.4 OUTCOME ASSESSMENT:

It is the time to event analysis. The event of interest (endpoint) will be discharge from the hospital. Time origin is the date of admission to the hospital. Survival time is the length of hospital stay, i.e. time interval in days measured from the day of admission to final discharge from the hospital. We anticipate we will be observing the event in all the patients admitted to the hospital within 30 days of admission (patient follow up time). If the event is not recorded in medical records as day of discharge from the hospital, then observation will be considered censored at last day of available record in the system. Patient will also be censored if patient died of any cause during hospitalization or if the patient is still in the hospital at the end of the calendar study time of study December 31, 2015.

2.5 EXPOSURE ASSESSMENT:

Exposure of interest is the after hospitalization first twenty-four hours maximum urine output (in milliliters). It will involve abstraction of the data from medical records within first twenty-four hours when the patient was either in the Emergency Room, medical floor or Cardiac Care Unit. Urine output initially will be measured as a continuous variable but later it will be dichotomized into two categories as aggressive diuretic therapy group (with urine output greater than 2400mL/1st 24 hours) and non-aggressive diuretic therapy group (with urine output less than or equal to 2400mL/1st 24 hours).

2.6 COVARIATE ASSESSMENT:

Data for covariates will be abstracted from the medical record (see table Variable Description table 1). Apart from demographic characteristics, data will be obtained about the type of CHF i.e. systolic or diastolic type of CHF, Ejection Fraction (EF) of the left ventricle, systolic blood pressure and serum creatinine at the time of admission. Creatinine will be further dichotomized into two categories to define stages of Chronic Kidney Disease (CKD) i-e less than or equal to Stage III CKD (lesser than 1.6mg/dL) and equal or greater than Stage IV CKD (higher than 1.6mg/dL). The total maximum dose of loop diuretics exclusively Furosemide given either as an intravenous bolus or continuous intravenous infusion in first twenty-four hours will be noted. Information regarding any adverse events occurred during hospitalization will be recorded which will include death, arrhythmia, worsening of renal function and hypotension.

Table 1 Variable Description

Variable Name	Description of Variable	Type of Variable
ID	Patient ID	
AGE	Age in years at the time of admission.	Continuous
SEX	Gender of the patient 0 =Female 1 =Male	Dichotomous
RACE	Race of the patient 0 = white 1 =non-white	Dichotomous
EVENT	Event of interest is the discharge from the hospital. 1 = Discharge from the hospital. 0 = Censored. No record of discharge from the hospital or patient died during hospitalization, or patient still in the hospital when study calendar time or patient follow up time ended.	Dichotomous
TIME	Time measured in number of days from the time of admission (origin) to the hospital to the day of discharge (event) from the hospital.	Continuous
FUROSEMI DE	The generic name of a type of a loop diuretic used. It denotes total 24-hour dose of Furosemide in mg given either IV continuous or IV Bolus in 1 st 24 hours.	Continuous
URINE	Total first twenty-four-hour urine output measured in mL after admission to the hospital.	Continuous
URINECAT	Total 1st 24-hour urine output measured in mL after admission to the hospital divided into 0 =Non-aggressive Diuresis (less than or equal 2400mL urine output in 1 st 24-hour)	Dichotomous

	1=Aggressive Diuresis (more than 2400mL urine output in 1st 24-hour).	
CR	Serum creatinine measured in mg/dL on the day of admission to the hospital.	Continuous
CRCAT	Serum Creatinine dichotomized into two categories 0 = less than or equal 1.6mg/dL (equivalent to stage 3 or less kidney disease) 1 = greater than 1.6 mg/dL (equivalent to stage 4 or greater kidney disease)	Dichotomous
EF	Ejection fraction of the left ventricle of heart on echocardiography (%).	Continuous
BP	Systolic blood pressure at the time of admission to hospital in mmHg.	Continuous
CHF	Type Congestive Heart Failure(CHF). 0 = Systolic CHF 1 =Diastolic CHF	Dichotomous
WORSEKID	Worsening of kidney function during hospitalization. It is defined as 0.3 mg/dL increase in the creatinine or 50% increase in the creatinine from baseline (admission day) in 1 st 24 hours.	Dichotomous
NEY		
ARRHYTH	Defined as atrial or ventricular tachyarrhythmia lasting greater than one minute.	Dichotomous
MIA	0 =No 1 =Yes	
DEATH	All-cause death from any cause. 0 =No 1 =Yes	Dichotomous
HYPOTENS	Low blood pressure (less than 90mmHg) after 1 st 24 hours.	Dichotomous
ION	0 =No 1 =Yes	

2.7 SAMPLE SIZE AND POWER:

Study size and power estimate will be based on the median number of days of hospital stay using the Log-Rank test method. Previously studies have noted median hospital stay of 7 days.⁴ We expect this median hospital stay in the hospital for the non-aggressive cohort (to be reference group). We anticipate clinically crucial minimum effect size of 3 three-day difference. The Type I error level is chosen as 0.05 for the two-sided hypothesis. The hospital has about 450 admissions with primary diagnosis of CHF each year. If we exclude 200 patients as a liberal guess not meeting inclusion criterion, then, we still have 100 patients in each arm which will give us the power of more than 0.90.

The details of the Log-Rank test method were applied using SAS (see Appendix). Total study time will be one calendar year i-e January 1, 2014, to December 31, 2014. There will be no accrual period; patient follow up will be from the day of admission to the hospital to final discharge up to 30 days. It is anticipated that event of interest (discharge) will be observed in all the patients and there will be no correction for loss to follow-up, treatment discontinuation, and other forms of censoring.

SAS PROGRAM CODING AND OUTPUT:

```

PROC POWER;
TWOSAMPLESURVIVAL TEST=LOGRANK
GROUPMEDSURVTIMES = (4 7)
  ACCRUALTIME = 0
  FOLLOWUPTIME = 30
  GROUPNS = 100 | 100
  POWER = .;
RUN;

```

Power analysis of Length of Hospital Stay and Aggressive vs non-Aggressive Diuresis:

The POWER Procedure
Log-Rank Test for Two Survival Curves

Fixed Scenario Elements	
Method	Lakatos normal approximation
Form of Survival Curve 1	Exponential
Form of Survival Curve 2	Exponential
Accrual Time	0
Follow-up Time	30
Group 1 Median Survival Time	4
Group 2 Median Survival Time	7
Group 1 Sample Size	100
Group 2 Sample Size	100
Number of Sides	2
Number of Time Sub-Intervals	12
Group 1 Loss Exponential Hazard	0
Group 2 Loss Exponential Hazard	0
Alpha	0.05

Computed Power
Power
0.970

STUDY TIME:

Stage 1: Review of medical Records 8 months.

Stage 2: Data collection and data analysis 1-2 months.

Stage 3: Presentation and publication 3-4 month.

2.8 DATA MANAGEMENT:

This is a retrospective review of medical records. Patient confidentiality will be maintained, and data will be de-identified. There will be no breach of subjects' privacy. The retrospective review does not involve patient's contact or consent since research does not involve more than minimal risk to subjects. Each patient will be assigned a unique identifier that will have no meaning to the study database (it will not incorporate subject name, medical record number). The patient identifier will be kept separately from main data. Principle investigator himself will transcribe data into the database. Only principle investigator and research mentors will have access to paper data entry forms and electronic database. Study database will be encrypted with a password, backed up regularly and will be stored offsite as well.

At the end of original study data, data dictionary and final data will be archived for three years for the investigator to respond to queries about the integrity of data or analysis. Any health care professional may request data provided University IRB approves it, and it complies with HIPAA. Principle investigator or research mentor may be contacted for this purpose. Patient data will be de-identified before that.

Missing values, outliers, and other data problems will be identified by using queries and will be cross-checked with medical records.

Crossfield validation will also be done for values within allowed ranges but inconsistent with one another.

We will maintain the audit log for all data changes. Editing procedure will be repeated with few errors identified, and then data will be finalized and or frozen so that no further changes can be made.

MISSING DATA:

Although every effort will be made to avoid missing data, patients with missing data will be compared to patients with complete data to describe potential bias due to differential loss of data. We will also explore methods for imputing missing data using maximum likelihood methods and will apply these in the presence of incomplete and missing data to reduce bias and increase the precision.

2.9 STATISTICAL ANALYSIS PLAN:

We propose to evaluate the association between aggressiveness of diuresis and length of hospital stay.

Univariate Analysis:

We will present the number and percent of subjects included in the study population before exclusion. Univariate analysis will be done to look for outliers and ranges. We will do normality test by using Shapiro Wilk test statistically and Q-Q plot

visually. Normally distributed data will be presented as mean and standard deviation and the non-normal data as median and interquartile(IQ) range. We will present categorical data as frequencies and percentages of the total.

Bivariate Analysis:

We will cross-tabulate covariates with exposure and outcomes for sensitivity analysis to address any potential bias and confounding. Cross with exposure (aggressive vs. non-aggressive group) will be evaluated with the Chi-square test to determine whether the observed distribution fits the expected distribution when the cell size is sufficient. When the cell size is not enough Fisher's exact test will be used. *P* values reflecting the differences in distribution will be presented for all the covariates. For continuous covariates, independent samples t-test will be used to compare the mean between two aggressive and non-aggressive groups for normally distributed data whereas Mann-Whitney U test will be used for non-normal data. Confidence intervals for the difference between two medians will be calculated using Hodges-Lehmann estimates.

Non-parametric Kaplan Meier method will be used to compare the proportion of patients discharged from the hospital (or 1- accumulated proportion of patient still in hospital) between aggressive versus non-aggressive diuresis group. Survival curves will be compared using Log Rank and Breslow tests. Cox proportional hazards regression will be used to calculate the univariate hazard ratio(HR) for the covariates significantly associated with mortality and length of hospital stay.

Multivariable analysis:

In multiple linear regression model we will define the predictors of 24-hour urine output by regressing the 24-hour urine output as a continuous outcome variable on 24 hours Furosemide dose including potential confounders in the model. We will include an interaction term between CKD and Furosemide. Backward Elimination method will be used to obtain the final model.

Cox proportional hazards regression analyses will be used to estimate Hazard Ratio and 95% CI for Hazard Ratio of hospital discharge in aggressive vs. non-aggressive diuretic therapy group. We will obtain variables for multivariable Cox proportional model via entry of all univariate baseline predictors of discharge from hospital with a value of $P < 0.2$ and predictors first twenty-four hours urine output from multivariable linear regression model mentioned earlier. Using backward selection and starting with a variable with the largest P value, we retained variables that altered the HR by $>10\%$ in the final model. Proportional-hazards assumption will be tested by visual inspection of log-minus-log survival plots and cumulative martingale residue plot. The main effects and all covariates found to be in violation of the proportional-hazards assumption will be appropriately transformed.

Statistical analysis will be performed with SPSS version 24.0 (SPSS Inc, Chicago, IL) and SAS version 9.4 (SAS Inst., Cary, NC) Significance will be defined as the 2-tailed value of $P < 0.05$.

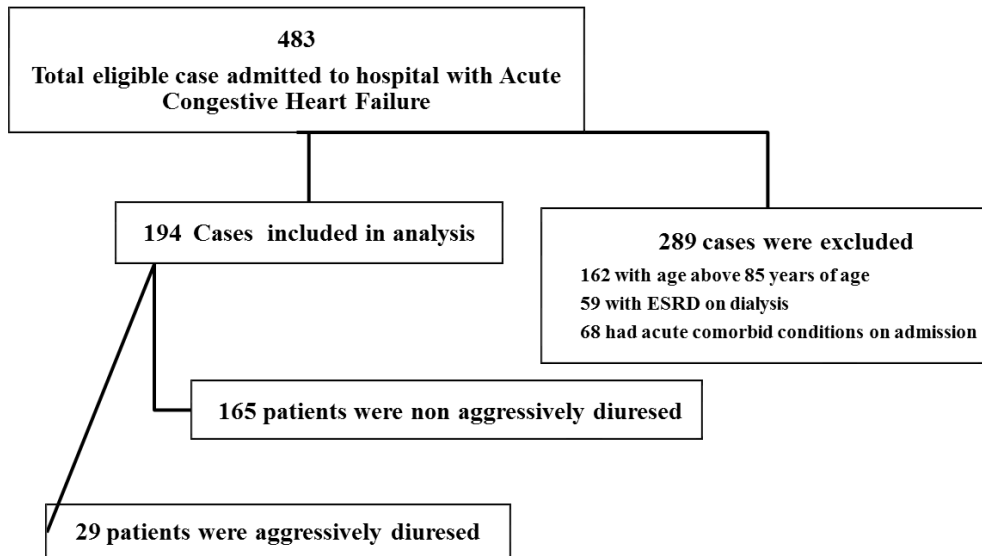


Figure 1: Flow chart of patients enrollment in study

RESULTS:

483 patients met screening criterion initially. We excluded 289 cases because of age above 80 years of age, dialysis dependent End Stage Renal Disease (ESRD) and other acute medical illness concurrently (See Figure1). 194 cases were included in the analysis. 165 met criterion of non-aggressive diuresis and 29 met criterion for aggressive diuresis. Follow up was complete in all cases. Six patients died in the non-aggressive group because of unrelated causes and were censored in time to event analysis.

In the total cohort, total first maximum twenty-four hours urine output ranged from 110ml to 5800mL with mean 1372 ± 1009 mL. Total maximum twenty-four hours Furosemide dose ranged from 40mg to 240mg with median dose 80 and IQ range of 40-80. Total range of length of hospital stay was 1 to 28 days with a median of 5 days and IQ range of 3-8 days.

Means of age ($P=0.09$), left ventricular ejection fraction ($P=0.78$) were comparable between aggressive and non-aggressive diuresis group. First twenty-four hours total dose of Furosemide used was significantly higher in aggressive diuresis groups as compared to non-aggressive diuresis group ($P=0.049$). Similarly, mean systolic blood pressure at admission (144 ± 23 versus 135 ± 23 ; $P=0.046$) and mean 24-hour urine output (3209 ± 903 versus 1049 ± 598 ; $P < 0.001$) were significantly higher in aggressive diuresis group than the non-aggressive group. Distributions of sex, race, and type of heart failure were comparable between two groups ($P > 0.05$). A smaller proportion of patients developed kidney dysfunction in non- aggressive diuresis group as compared to aggressive diuresis group, but it was not found to be statistically significant (6.9% versus

12.15%; $P = 0.2$). A smaller proportion of patients were found to have an episode of hypotension in the aggressive diuresis group as compared to the non-aggressive diuresis group, but it was not found to be statistically significant (6.9% versus 13.9 %; $P=0.38$). There were six deaths noticed in total in non-aggressive diuresis group only. Eight patients were noted to have an arrhythmia in the non-aggressive diuresis group as compared to 1 in aggressive diuresis group.

Table 2: Characteristics of Patients

Characteristics	Total Cohort	Non-aggressive diuresis^a	Aggressive diuresis^a	P value
Age(years)				
Mean(SD)	72(11)	72(10)	69(12)	0.09
Race				
White	182(93.8%)	153(92.7%)	29 (100%)	0.22
Non-white	12(6.2%)	12(7.3%)	0(0 %)	
Sex				
Male	96(49.5%)	80 (48.5%)	16 (55.2%)	0.51
Female	98(50.5%)	85 (51.5%)	13 (44.8%)	
Type of Congestive Heart Failure				
Systolic	112(57.7%)	96(58.2%)	16(55.2%)	0.76
Diastolic	82(42.3%)	69(41.8%)	13(44.8%)	
Left Ventricular Ejection Fraction (%)				
Mean(SD)	40(16)	40(16)	41(15)	0.78
Systolic Blood pressure on Admission (mmHg)				
Mean(SD)	137(23)	135(23)	144(23)	0.046*
Creatinine at Time of Admission mg/dL)				
Mean(SD)	1.33(0.57)	1.33(0.56)	1.31(0.63)	0.86
Dose of Furosemide used(mg) †				
Median(IQ)	80(40-80)	70(40-80)	80(55-120)	0.049*
24 Hour Urine output(mL)				
Mean(SD)	1372(1009)	1049(598)	3209(903)	<0.001*
Worsening of Kidney Function				
Yes	22(11.3%)	20 (12.15%)	2(6.9%)	0.54
No	172(88.7%)	145(87.9%)	27(93.1%)	
Hypotension				

Yes	25(12.9%)	23(13.9%)	2(6.9%)	0.38
No	169(87.1%)	142(86.1%)	27(93.1%)	
Death				
Yes	6(3.1%)	6(3.6%)	0(0%)	0.59
No	188(96.9%)	159(96.4%)	29(100%)	
Arrhythmia				
Yes	9(4.6%)	8(4.8%)	1(3.4%)	1
No	185(95.4%)	157(95.2%)	28(96.6%)	

P value refers to the difference between aggressive and non-aggressive diuresis groups.

*Significant

†Loop diuretic dose reported as median with interquartile range; all other values represent mean±SD or %.

The final multivariable linear regression model after backward elimination showed statistically significant main effect ($P<0.001$) of a dose of Furosemide in increasing first twenty-four hours urine output along with its interaction with creatinine at the time of admission, depicting higher dose of Furosemide required to produce the same amount of urine with greater than 1.6mg/dL creatinine on admission. ($P=0.02$). See Fig 2, Table 3.

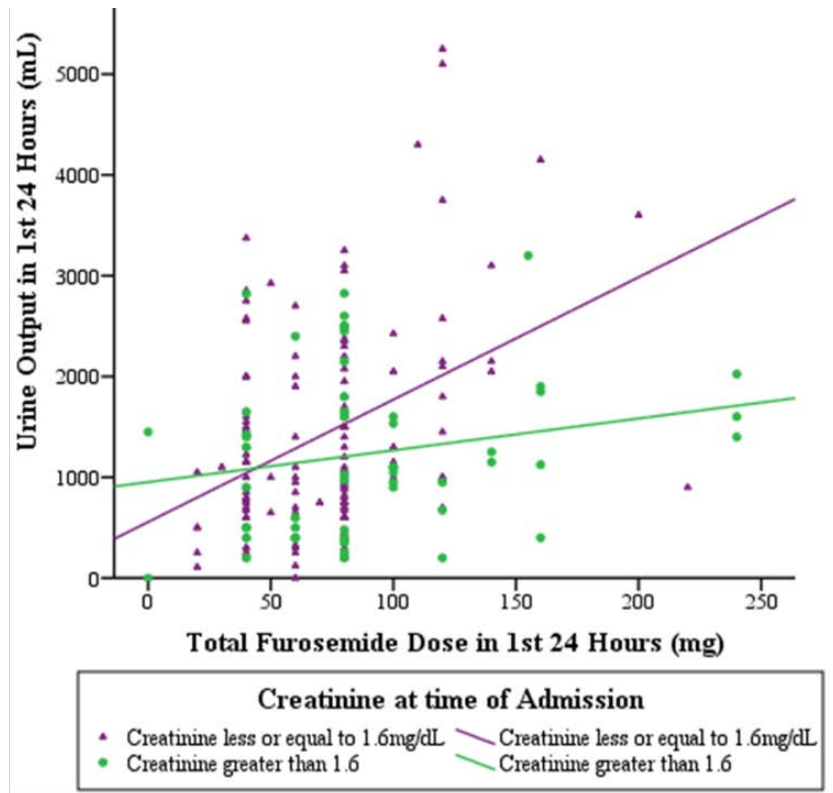


Figure 2: Scatter plot with regression line for relationship between total dose of Furosemide used in 1st 24 hours, urine output in 1st 24 hours in patients with less than/equal to 1.6mg/dL and greater than 1.6mg/dL serum creatinine levels at admission.

Table 3: Multiple Linear Regression model with 24 Hour Urine output regressed on Dose of Furosemide, Creatinine at the time of Admission

Characteristics	Coefficient	Standard Error	95% CI	t	P
intercept	556.88	190.91	180.31 to 933.45	2.91	0.004
Furosemide	12.14	2.43	7.35 to 16.94	5.00	<0.001*
Cr > 1.6	395.26	322.42	-240.73 to 1031.25	1.23	0.22
Cr >1.6 X Furosemide	-8.98	3.47	-15.83 to -2.14	-2.59	0.02*

Furosemide, Total 24 hours dose of Furosemide used in 24 hours; Cr>1.6, indicates greater than 1.6 mg/dL serum creatinine at time of admission equivalent to stage 3 or less kidney disease; Cr>1.6 X Furosemide, indicates interaction between furosemide and creatinine greater than 1.6mg/dL.*Significant

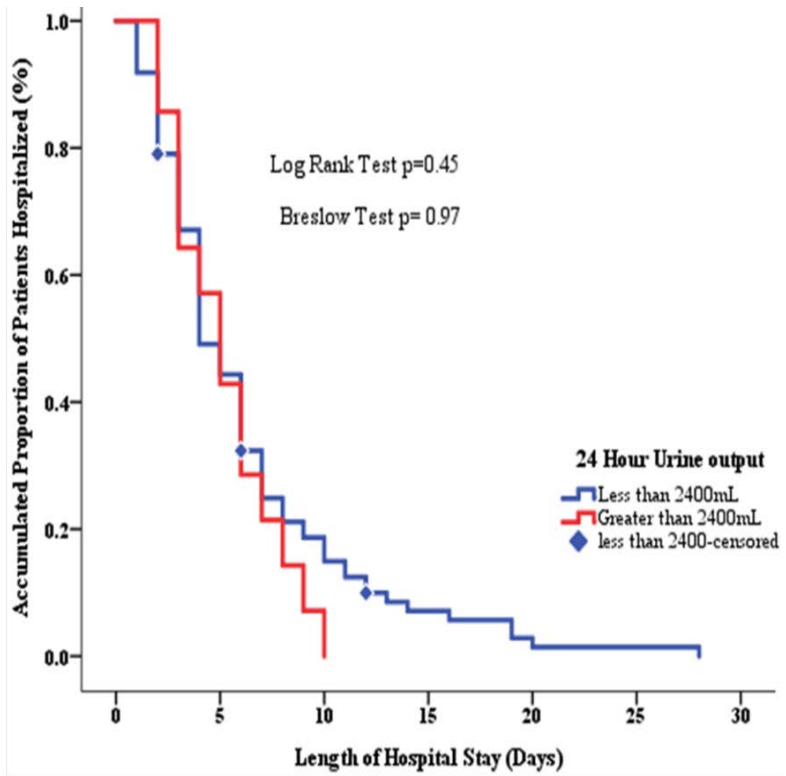
Kaplan Meier estimate of the median accumulated proportion of patients still in hospital in aggressively diuresed patients(n=29) was 4 days as compared to 5 days in non-aggressively diuresed patients (n=165). Log-Rank test ($P=0.67$) and Breslow test (0.77) revealed non-significant differences between the accumulated hospitalized proportion over time.

Table 4 Summary of Kaplan – Meir Estimate for Cohort- total Study Sample of 194 Patients

Time (days)	Accumulated Proportion patient in Hospital (%)	95% CI (%)	Number of patients discharged	Number patients censored	Number at Risk
2	0.80	0.74 to 0.86	38	0	156
4	0.53	0.45 to 0.61	91	2	101
6	0.32	0.26 to 0.38	131	0	61
8	0.20	0.15 to 0.26	153	1	38
10	0.15	0.09 to 0.21	163	1	27

Table 5 Survival Characteristics of subgroup of Study Sample

Group	No of total Patients	Total Number of Patients Discharged	Total Number Censored	Median Hospital stay in days 95% (CI)
Aggressive diuresis	29	29	0	4 (2.95 to 5.06)
Non-aggressive Diuresis	165	159	6	5 (4.40 to 5.60)



Group	Number at Risk					
Urine lesser or equal to 2400mL	86	37	12	5	1	0
Urine greater than 2400mL	14	7	9	0	0	0

Figure 3 : Comparison of length of stay in hospital(days) for patient with acute Congestive Heart Failure with urine output less than or equal to 2400mL/24hours and greater than 2400mL/24Hours.

Table 6 Univariate Cox Proportional Hazards Regression Model Showing effect of Aggressive Diuresis on Risk of Discharge from Hospital.

Characteristics	Coefficient	Standard Error	Wald χ^2	<i>P</i> value	Hazard Ratio	95% CI
Aggressive diuresis	0.079	0.20	0.15	0.70	1.08	0.73 to 1.61

Table 7: Cox Proportional Hazards Regression Model Showing the Effect of Four Variables on Risk of Discharge from Hospital

Characteristics	Coefficient	Standard Error	Wald χ^2	P value	Hazard Ratio	95% CI
Aggressive diuresis	0.11	0.21	0.27	0.60	1.12	0.74 to 1.68
LVEF	0.007	0.005	2.19	0.14	1.01	1.00 to 1.017
Furosemide	<0.001	0.003	0.001	0.98	1.000	0.995 to 1.005
Cr >1.6	-0.10	0.33	0.10	0.75	0.90	0.47 to 1.72
Cr >1.6 X Furosemide	0.001	0.004	0.07	0.79	1.001	0.99 to 1.01

Aggressive diuresis, indicates greater than or equal 2400mL/ 24 Hour urine; LVEF, Left Ventricular Ejection Fraction; Furosemide, Total 24 hours dose of furosemide used in 24 hours; Cr>1.6, indicates greater than 1.6 mg/dL serum creatinine at time of admission equivalent to stage 3 or less kidney disease; Cr>1.6 X Furosemide, indicates interaction between furosemide and creatinine greater than 1.6mg/dL.

In univariate analysis, Cox proportional hazards regression showed the unadjusted hazard rate of discharge from hospital was similar to patients with aggressive diuresis, as results did not approach statistical significance (HR=1.08; $P=0.70$). Similarly, in multivariate Cox model creatinine at the time of admission when greater than 1.6mg/dL ($P=0.75$), left ventricular ejection fraction ($P=0.14$), total 24 hours dose of furosemide given ($P=0.98$) and interaction between Furosemide and Creatinine ($P=0.79$) were not statistically significant. The hazard rate of discharge from Hospital was 12% higher in aggressive diuresis group than non-aggressive diuresis but still statistically non-significant (adjusted HR=1.12; $P=0.6$).

DISCUSSION:

A diuretic is a primary agent used in acute CHF. The effect of a diuretic on urine output is modified by patient-related comorbidities and concurrent administration of other medications. It is a common observation that the dose required for the same amount of diuresis varies not only between patients with similar comorbidities but additionally within the same patient during different hospitalizations. Loop diuretics over a period can lead to diuretic resistance with persistent fluid overload. It is likely from the activation renin-angiotensin-aldosterone system and sympathetic nervous system, hence reducing renal blood flow, decreasing the filtered sodium and increasing its reabsorption. Chronic loop diuretic therapy also leads to hypertrophy of epithelial cells in the distal tubules thus increasing sodium absorption^{9,10}. Other factors responsible are decreased drug delivery to nephron and hyperchloremia.¹¹ These mechanisms make dose response unpredictable. Despite this heterogeneity in responses, ROSE randomized controlled trial which recruited patients with advanced heart failure showed the effect of diuresis of loop

diuretic to be unchanged even if combined with other medications. In this RCT one of the primary endpoints was the 72-hour cumulative urine volume as an index of diuresis. After 72-hours study investigators did not find a difference in total median dose of diuretic required as well as cumulative urine output in three combination groups (placebo with furosemide, low-dose dopamine with furosemide, and low-dose nesiritide with furosemide).^{6,12} Extending the same concept to our study and ignoring the use of other medication, as expected the group with higher diuresis (aggressive diuresis group) had a higher median dose of diuretic than the non-aggressive group. We found a linear relationship between the loop diuretic dose and first twenty-four hours urine output modified by worse kidney dysfunction. As higher urine output would lead to early relief of symptoms with congestion, we expected an earlier discharge of a patient with higher first twenty-four hours urine output, however to our surprise, there was no statistically significant difference between the hazards of discharge of the patients in two groups. There appeared to be a disconnect, as high diuresis achieved in first twenty-four hours did not translate into a shorter hospital stay. There can be many explanations. Length of hospital stay might have been affected by the subsequent different daily dose of diuretic depending on the clinical course. Patients in the non-aggressive diuretic therapy group with lesser urine output might have had incomplete relief of congestion, and in turn had to be given smaller doses for a longer period thus increasing the length of hospital stay. On the other hand, the patients who were in the aggressive diuresis therapy group might have had adverse effects as worsening of kidney function, hypotension or electrolyte disturbances, notorious with a higher diuretic dose thus might have required subsequent dose reduction leading to less urine output.¹³⁻¹⁶ Number of adverse effect in each group

are not reliable in our study as these were counted in the first twenty-four hours only and study was not powered to detect the adverse outcome difference. It appears that the advantage of increased urine output in the first twenty-four hours was offset by the low urine output in subsequent days, leading to comparable total days of hospital stay.

Secondary analysis of ESCAPE trial showed that when aggressive diuretic therapy was used, excess reduction in the intravascular volume measured by surrogate markers of hemoconcentration and protein concentration directly correlated with worsening of kidney function. After aggressive diuresis with higher dose there was a greater change in weight (fluid loss) leading to decrease in pulmonary wedge pressure and right atrial pressure, as well as poor perfusion to kidneys and worsening kidney function likely explaining cardiorenal syndrome.¹⁷ Similarly, a higher dose of loop diuretic theoretically leads to hemodynamic disturbance causing hypotensive episodes due to reduced cardiac index and reduction in filling. DOSE trial used a 2-by-2 factorial design to test Furosemide in low vs. high dose as a continuous IV vs. bolus IV dose to find a difference in primary endpoints of improvement in patient symptoms and worsening of renal function in any specific group.⁷ The study found no difference in primary endpoints as well as a one of its prespecified secondary endpoint; the length of hospital stay. Since our study has shown a linear relationship between urine output and the dose of Furosemide modified by baseline creatinine, we can safely argue that there was higher urine output in high dose arm of Furosemide DOSE trial as there was no difference in baseline creatinine in any group. Despite higher urine output, it did not result in a shorter hospital stay. It corresponds with our finding that amount of diuresis predicts the degree of decongestion and relief of symptoms better than the surrogates; the

amount of loop diuretic used directly. The amount of urine output still does not influence the length of hospital stay. Howard and Dunn conducted a non-randomized prospective study on >65-year old patient with NYHA class IV CHF. Treatment arm involved aggressive diuretic therapy in achieving the goal of $\geq 2400/24$ hours urine output. This lead to a shorter hospital stay of 2.3 days and lesser cost than the non-aggressive (standard medical care group). Results in that study are appealing but likely biased due to the use of particular subset population in the treatment group, a small sample of 17 only, non-randomized design and differential close monitoring of the intervention group for the signs of decongestion, adverse effects as well as prompt replacement of electrolytes especially chloride to avoid resistance.³ Li and Hong in China conducted a similar retrospective cohort study design on 195 patients. After implementing same cutoffs to define the aggressive diuretic therapy as urine output of $\geq 2400\text{mL}/24$ hour, they found a shorter length of hospital stay (aggressive diuretics therapy: 11 days vs. non-aggressive therapy: 16 days; $P < 0.05$).⁸ Although the study has a similar design as our study results are different possibly because the average length of hospital stay in their groups was 13.5 days much higher than our mean duration of 5 days for our total study cohort. It is likely related to the intrinsic difference in population or treatment difference in two countries. In ESCAPE Trial, aggressive diuresis using the pulmonary wedge pressure based monitoring method vs standard clinical assessment method did not show significant difference in endpoint of total 6 months mortality after randomization as well as difference in prespecified endpoint of mean number of days hospital stay (aggressive diuretics therapy: 8.7 days vs non aggressive therapy : 8.3 days; $P = 0.67$). There was no comparison of the urine output in the groups, but we can argue that pulmonary wedge

pressure directed group had higher urine output, but still there was no difference in length of hospital stay^{17,18}.

LIMITATIONS:

Our study has inherent limitations of any retrospective study. Since it not prospective blinded RCT study and all patient were a subset of all acute CHF patient from a single center meeting inclusion criterion, results of this study might have some selection bias and all unknown confounders might not have been controlled. Patients were included with first-time hospital admission or on readmission with a primary diagnosis of acute CHF, but other coexistent comorbidities potentially complicating the hospital course were not included. We did not have data on weight, dietary sodium and fluid intake, or BNP levels in patients at the time of admission. Since diuretic dose and urine output was limited to first twenty-four hours and not during complete hospital course, it limits the ability to determine the temporal relationship between urine output and length of hospital stay. The proportion of patient in each group were not equal as expected during the assessment of the power of study, thus it will affect the actual total power study was able to achieve.

CONCLUSION:

To date, clinicians have no clear evidence-based strategies for safely and rapidly improving congestion in patients with acute CHF. Our study showed higher diuretic dose based on the inherent desire to increase diuresis for a quicker relief of symptoms is associated with higher urine output and possibly untoward adverse effects during the

hospital course. Thus patients with higher and low urine output tend to stay a comparable total number of days in the hospital. Although these results are in line with the possible pathological mechanism, there were methodological limitations with small sample size. As a result, we suggest challenging rather than changing current conceptions about monitoring the diuresis in a patient with dose of loop diuretic rather than the amount of urine output. Future research necessary in large prospective randomized controlled trials to assess the direct effect of amount diuresis rather than the dose of diuretics in the relief of signs or symptoms or radiological improvement in congestion, readmission, mortality, biochemical parameters and cost of hospital admission. We suggest an adequate dose of diuretic to keeping the goal of daily diuresis less than 2400mL/24 hours.

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