New York Science Journal

Websites:
http://www.sciencepub.net/newyork
http://www.sciencepub.net

Emails:
newyorksci@gmail.com
editor@sciencepub.net

MARSLAND PRESS
Multidisciplinary Academic Journal Publisher

Sequential Nephron Blockade with Metolazone for Decongestion in Advanced Decompensated Heart Failure

Arafat M. Abd Elrahman, and Muhammad A. Alghorayeb

National Heart Institute, Giza, Egypt
Corresponding email: Arafatmahmoud88@yahoo.com

Abstract: Background: Congestion-driven hospitalization remains a major cause of morbidity and mortality in patients with acute decompensated heart failure (ADHF). Diuretic resistance frequently limits the effectiveness of loop diuretics, prompting the use of sequential nephron blockade with thiazide-like diuretics such as metolazone. Objective assessment of decongestion using radiographic markers may improve evaluation of treatment response. **Objectives:** To compare diuretic response, radiographic and clinical decongestion, renal safety, and short-term clinical outcomes in patients with advanced decompensated heart failure treated with intravenous loop diuretics alone versus loop diuretics plus metolazone. **Methods:** This retrospective observational cohort study included 43 patients with chronic heart failure with reduced ejection fraction hospitalized for ADHF. Patients were treated with intravenous Frusemide alone (n = 23) or in combination with metolazone (n = 20). Diuretic efficiency, urine output, weight change, congestion score index (CSI) derived from chest radiography, renal function, electrolyte changes, loop diuretic dose at discharge, and survival were evaluated. **Results:** Patients receiving metolazone demonstrated significantly greater diuretic efficiency (958.00 ± 156.46 mL/40 mg Frusemide vs, 614.35 ± 281.66 mL/40 mg; $p < 0.05$), higher urine output (2950.00 ± 591.61 mL vs 2165.22 ± 939.83 mL; $p < 0.05$), and larger reductions in body weight compared with Frusemide alone (−5.96 ± 2.20 kg) vs., −3.65 ± 1.38 kg; $p < 0.05$).(all $p < 0.05$). Radiographic decongestion was more pronounced in the metolazone group, with a significantly greater reduction in CSI at discharge (1.15 ± 0.37 vs 0.74 ± 0.54; $p < 0.05$). The metolazone group required a significantly lower loop diuretic dose at discharge (252.39 ± 137.05 mg; $p < 0.05$), without an increase in renal dysfunction or electrolyte disturbances. Although survival was numerically longer in the metolazone group, the difference was not statistically significant. **Conclusion:** In patients with advanced ADHF, adjunctive metolazone therapy was associated with improved diuretic efficiency, more effective radiographic and clinical decongestion, and lower loop diuretic requirements at discharge, without compromising renal safety.
[Arafat M. Abd Elrahman, and Muhammad A. Alghorayeb **Sequential Nephron Blockade with Metolazone for Decongestion in Advanced Decompensated Heart Failure.** *N Y Sci J* 2026;19(3):1-9]. ISSN 1554-0200 (print); ISSN 2375-723X (online). http://www.sciencepub.net/newyork. 01. Doi: 10.7537/marsnys190326.01

Keywords: diuretic resistance, decongestion, heart Failure, metolazone, radiological congestion score index (RCSI)

1. Introduction

Acute decompensated heart failure (ADHF) remains a leading cause of hospitalization among patients with chronic heart failure with reduced ejection fraction (HFrEF) and is associated with substantial morbidity and mortality. The predominant driver of hospital admission is worsening congestion resulting from pulmonary and systemic volume overload, which contributes to severe symptoms, prolonged length of stay, frequent rehospitalization, and adverse short- and mid-term outcomes. Consequently, effective decongestion during hospitalization represents a cornerstone of ADHF management and a critical determinant of prognosis (1-3).

Intravenous loop diuretics constitute the first-line therapy for volume removal in ADHF; however, an inadequate diuretic response is frequently encountered, particularly in patients with advanced HFrEF. Diuretic resistance, characterized by impaired natriuresis and insufficient decongestion despite appropriate loop diuretic dosing, poses a significant clinical challenge. Its pathophysiology is multifactorial, involving reduced renal perfusion, neurohormonal activation, altered drug pharmacokinetics, and enhanced distal tubular sodium reabsorption.(4-6). In clinical practice, management often requires escalation of loop diuretic doses or implementation of sequential nephron blockade using thiazide-like diuretics, most commonly metolazone. While this strategy may augment diuresis and symptom relief, it carries a heightened risk of worsening renal function and electrolyte disturbances, particularly in patients with pre-existing renal dysfunction (7-9).

Accurate assessment of congestion remains challenging, as clinical signs and symptoms may underestimate residual volume overload. Persistent subclinical congestion at discharge is common and strongly associated with early readmission and adverse outcomes.(10) Chest radiography is routinely

performed in hospitalized heart failure patients and provides objective information on pulmonary congestion. The congestion score index (CSI) offers a standardized and reproducible method for quantifying radiographic congestion and has demonstrated independent prognostic value beyond conventional clinical assessment (3).

In this context, objective markers of diuretic response are increasingly recognized as valuable tools to guide therapy. Diuretic efficiency, defined as urine output relative to loop diuretic dose, has emerged as a practical indicator of treatment response and may help identify patients at risk of poor decongestion or treatment-related complications (3).

Accordingly, the present study aimed to evaluate diuretic response, radiographic and clinical decongestion, renal safety, and short-term clinical outcomes in patients hospitalized with advanced decompensated HFrEF in a real-world tertiary care setting. By integrating measures of diuretic efficiency and radiographic congestion, this study seeks to provide clinically relevant insights to optimize decongestive strategies and improve outcomes in this high-risk population.

2. Patients and Methods

This was a retrospective observational cohort study conducted at heart failure unit in a tertiary health care center. All consecutive adult patients admitted with advanced decompensated heart failure and evidence of significant volume overload were enrolled between November 2024 and April 2025

Inclusion criteria were: any patient aged ≥ 18 years know to be chronic heart failure with reduced ejection fraction (< 40%) presented with acute decompensated heart failure with clinical signs of congestion (NYHA class III or IV) with requirement for intravenous loop diuretic therapy.

Patients were excluded from the study if they developed acute coronary syndrome during admission, had end-stage renal disease requiring dialysis, or presented with severe baseline electrolyte imbalances. Additional exclusion criteria included cardiogenic shock, the need for high-dose inotropic support, incomplete clinical or laboratory data, and pregnancy

Demographic, clinical, laboratory, and echocardiographic data were extracted from medical records. Collected variables included age, sex, body mass index (BMI), heart failure etiology, comorbid conditions (hypertension, diabetes mellitus, dyslipidemia, ischemic heart disease, atrial fibrillation, valvular disease, cardiomyopathy, and chronic kidney disease), and baseline heart failure medications.

Baseline laboratory assessments included serum creatinine, blood urea, estimated glomerular filtration rate (eGFR), serum sodium, and potassium. Left ventricular ejection fraction (LVEF) was obtained from transthoracic echocardiography performed during hospitalization.

All patients received intravenous Frusemide upon admission. The choice to add metolazone (typical dose 2.5–10 mg daily) was at the discretion of the treating physician, typically in cases of inadequate diuretic response or persistent congestion.

Diuretic doses were recorded daily. Diuretic efficiency was calculated as urine output per 40 mg of Frusemide equivalent. Total urine output, body weight change during hospitalization, and loop diuretic dose at discharge were documented.

Clinical congestion was assessed using the congestion score index (CSI) at admission and at discharge. The change in CSI (ΔCSI) was calculated to quantify decongestion during hospitalization. Higher CSI values indicate more severe congestion.

Radiographic CSI was used to quantify the severity of pulmonary congestion in CXR as previously published [18,19]. Each lung field os divided into 6 zones. A score of 0-3 is assigned for each area where; Score 0, no congestion sign; Score 1, cephalization (superior area), perihilar haze or perivascular/peri-bronchial cuffing, or Kerley A lines (middle area), Kerley B, or C lines (inferior area); Score 2, interstitial or localized/mild alveolar pulmonary edema; Score 3, intense alveolar pulmonary edema. To enhance the reproducibility of the severity of confluent edema, a portion of the divided lung fields which was visually similar to the cardiac silhouette was regarded as an intense zone, whereas the field with weaker density was regarded as a mildly intense zone. Lung areas were not scored when more than one-third of the divided lung fields were occupied by pleural effusion (including vanishing tumor), atelectasis, or cardiac silhouette. CSI was calculated as the sum of the scores in each zone divided by the number of available zones (11-13).

Diuretic efficiency was calculated as net urine output (mL) per 40 mg of Frusemide equivalent. Daily diuresis volume, body weight change, and loop diuretic requirements were recorded during hospitalization. Renal function (serum creatinine, eGFR, blood urea) and electrolytes were monitored at admission and discharge.

All Patients were followed after discharge for recurrent hospital admission up to 6 months.

The primary outcome of the study was to assess the diuretic response, which was measured through three key parameters: diuretic efficiency, total urine output, and the change in body weight. Additionally, the study aimed to evaluate secondary outcomes, including changes in renal function and electrolytes at

discharge, the optimal loop diuretic dose at discharge, the severity of congestion, and overall survival during follow-up.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation or median with interquartile range, as appropriate. Categorical variables are expressed as frequencies and percentages. Comparisons between groups were performed using: student's t-test or Mann–Whitney U test for continuous variables and Chi-square or Fisher's exact test for categorical variables. Survival outcomes were analyzed using Kaplan–Meier curves. A p-value < 0.05 was considered statistically significant. Statistical analyses were performed using standard statistical software. SPSS version 26 was used for al statistical analysis.

3. Results

Baseline Characteristics

A total of 43 patients were included in the analysis, with 23 patients in the Frusemide group and 20 patients in the metolazone group. Baseline demographic and clinical characteristics were well comparable between the two groups, with no statistically significant differences observed (Table 1).

The mean age of the study population was 71.67 ± 8.12 years, and the majority of patients were male (79.1%). Mean body mass index was comparable between groups (27.74 ± 3.82 kg/m² in the Frusemide group vs 28.00 ± 3.74 kg/m² in the metolazone group; $p = 0.823$).

The prevalence of comorbidities, including hypertension (76.7%), dyslipidemia (46.5%), diabetes mellitus (27.9%), cardiomyopathy (51.2%), ischemic heart disease (39.5%), atrial fibrillation (32.6%), valvular heart disease (9.3%), and chronic kidney disease (53.5%), was similar between groups (all $p > 0.05$).

Baseline renal function and electrolyte parameters did not differ significantly between groups. Mean serum creatinine on admission was 1.93 ± 0.53 mg/dL in the Frusemide group and 1.90 ± 0.54 mg/dL in the metolazone group ($p = 0.849$), with comparable estimated glomerular filtration rate (eGFR) values (39.57 ± 10.95 vs 40.50 ± 10.81 mL/min/1.73 m²; p = 0.78). Baseline serum sodium and potassium levels were also similar.

Cardiac function and clinical status at presentation were comparable, with mean ejection fraction of 34.86 ± 4.90% overall ($p = 0.235$). Most patients presented with advanced heart failure symptoms, with 46.5% classified as NYHA class III and 53.5% as NYHA class IV, without significant intergroup differences ($p = 0.425$).

All patients were on anti-heart failure therapies, including ACE inhibitors, ARBs, beta-blockers, mineralocorticoid receptor antagonists, digoxin, and ARNI, were evenly distributed between the two groups (all $p > 0.05$). The loop diuretic dose at admission was also similar (266.74 ± 109.81 mg vs 268.25 ± 107.95 mg; P = 0.964).

Patients treated with metolazone demonstrated a significantly greater diuretic efficiency compared with those receiving Frusemide alone (958.00 ± 156.46 mL/40 mg Frusemide vs, 614.35 ± 281.66 mL/40 mg; $p < 0.05$) (Fig. 1A).

Similarly, the mean diuresis volume was significantly greater in the metolazone group (2950.00 ± 591.61 mL vs 2165.22 ± 939.83 mL; p < 0.05) (Fig. 1B).

Weight reduction during hospitalization was significantly dropped in the metolazone group (−5.96 ± 2.20 kg) compared with the Frusemide group (−3.65 ± 1.38 kg; p < 0.05) (Fig. 1D).

Renal Function and Electrolytes at Discharge

At discharge Blood urea levels were significantly lower in the metolazone group (64.75 ± 13.76 mg/dL) compared with the Frusemide group (85.22 ± 25.12 mg/dL; p < 0.05). However, there were no significant differences between groups in serum creatinine ($p = 0.405$) or eGFR ($p = 0.618$).

Serum potassium and sodium levels at discharge remained comparable between groups, with no statistically significant differences observed (Table 2).

Loop Diuretic Dose and Congestion Score

At discharge, patients in the metolazone group required a significantly lower loop diuretic dose (155.00 ± 59.16 mg) compared with those in the Frusemide group (252.39 ± 137.05 mg; p < 0.05) (Table 2).

Congestion Severity Index (CSI) at admission did not differ significantly between groups ($p = 0.120$). However, at discharge, CSI was significantly lower in the metolazone group (0.55 ± 0.69) compared with the Frusemide group (1.35 ± 0.93; p < 0.05). The reduction in CSI (ΔCSI) was significantly greater in the metolazone group (1.15 ± 0.37 vs 0.74 ± 0.54; p< 0.05), indicating more effective decongestion (Fig.1 C).

Kaplan–Meier estimates demonstrated longer survival in metolazone compared with Frusemide Group. The mean survival time in Frusemide group was 99.8 months (SE 11.0; 95% CI 78.2–121.4), In contrast, metolazone group had a mean survival time of 133.0 months (SE 13.8; 95% CI 105.9–160.1). Although Group 2 exhibited numerically longer survival times, these differences did not reach statistical significance (p = 0.26) (Fig. 2).

New York Science Journal

Websites:
http://www.sciencepub.net/newyork
http://www.sciencepub.net

Emails:
newyorksci@gmail.com
editor@sciencepub.net

MARSLAND PRESS
Multidisciplinary Academic Journal Publisher

Table (1): Patient characteristics OF Frusemide and Metolazone Groups.

		Frusemide group (23 patients)	Metolazone group (20 patients)	Total (43 patients)	P value
Age		72.04±8.28	71.25±8.12	71.67±8.12	0.753
GENDER	Males	18 (78.3%)	16 (80%)	34 (79.1%)	0.889
	Females	5 (21.7%)	4 (20%)	9 (20.9%)	
BMI (kg/m^2)		27.74±3.82	28.00±3.74	27.86±3.74	0.823
Hypertension		18 (78.3%)	15 (75%)	33 (76.7%)	0.801
Dyslipidemia		11 (47.8%)	9 (45%)	20 (46.5)	0.853
Diabetes mellitus		7 (30.4%)	5 (25%)	12 (27.9)	0.692
Cardiomyopathy		12 (52.2%)	10 (50%)	22 (51.2%)	0.887
IHD		9 (39.1%)	8 (40%)	17 (39.5)	0.954
Valvular		2 (8.7%)	2 (10%)	4 (9.3%)	0.883
Atrial Fibrillation		7 (30.4%)	7 (35%)	14 (32.6%)	0.750
CKD		13 (56.5%)	10 (50%)	23 (53.5%)	0.669
EF%		35.70±4.85	33.90±4.91	34.86±4.90	0.235
Creatinine (On Admission)		1.93±0.53	1.90±0.54	1.91±0.52	0.849
eGFR (mL/min)		39.57±10.95	40.50±10.81	40±10.77	0.78
Urea (mg/dL)		82.35±24.70	73.35±16.59	78.16±21.56	0.175
K (mEq/L)		4.36±0.36	4.25±0.37	4.31±0.37	0.307
Na (mEq/L)		140.17±4.78	140.50±3.59	140.33±4.22	0.804
Systolic BP (mmHg)		146.83±13.70	141.95±12.61	144.56±13.28	0.234
Diastolic BP (mmHg)		80.57±7.66	79±6.91	79.84±7.28	0.489
NYHA	Class III	12 (52.2%)	8 (40%)	20 (46.5%)	0.425
	Class IV	11 (47.8%)	12 (60%)	23 (53.5%)	
Loop Diuretic Dose at Admission (mg/day)		266.74±109.81	268.25±107.95	267.44±107.65	0.964
ACEi		13 (56.5%)	11 (55%)	24 (55.8%)	0.920
ARBs		7 (30.4%)	6 (30%)	13 (30.2%)	0.975
Beta Blockers		14 (60.9%)	13 (65%)	27 (62.8%)	0.780
Digoxin		7 (30.4%)	5 (25%)	12 (27.9%)	0.692
MRA		10 (43.5%)	8 (40%)	18 (41.9%)	0.818
ARNI		3 (13%)	3 (13%)	6 (14%)	0853

Table (2): Decongestion effect in both Frusemide and Metolazone Groups.

	Frusemide group (23 patients) (Mean ± SD)	Metolazone group (20 patients) (Mean ± SD)	T test
Diuretic Efficiency (mL/40 mg Frusemide)	614.35 ± 281.66	958.00 ± 156.46	P< 0.05
Urea (mg/dL)	85.22 ± 25.12	64.75 ± 13.76	P < 0.05
eGFR (mL/min)	44.13 ± 18.37	41.40 ± 17.09	0.618
Creatinine (mg/dL)	1.83 ± 0.57	1.69 ± 0.56	0.405
K at Discharge (mEq/L)	4.04 ± 0.59	4.08 ± 0.56	0.817
Na at Discharge (mEq/L)	139.91 ± 5.28	138.65 ± 4.38	0.403
Mean Diuresis Volume (mL)	2165.22 ± 939.83	2950.00 ± 591.61	P < 0.05
Δ Weight	-3.65 ± 1.38	-5.96 ± 2.20	P < 0.05
Loop Diuretic Dose at discharge (mg/day)	252.39 ± 137.05	155.00 ± 59.16	P < 0.05
CSI at Admission	2.09 ± 0.79	1.70 ± 0.80	0.120
CSI at Discharge	1.35 ± 0.93	0.55 ± 0.69	P < 0.05
ΔCSI	0.74 ± 0.54	1.15 ± 0.37	P < 0.05

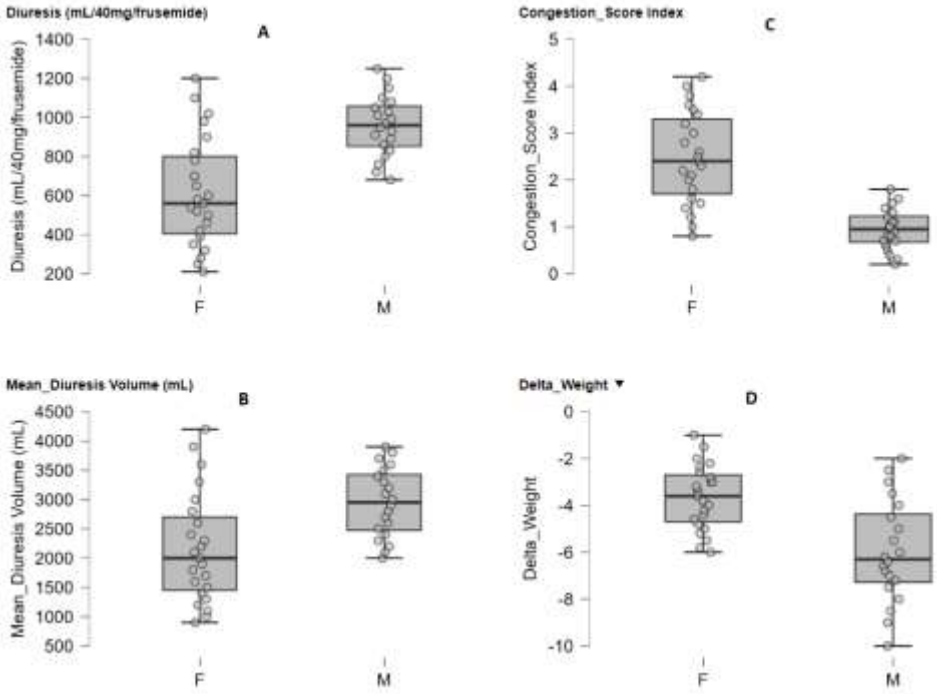

Fig. (1): Box plot of diuresis efficiency (A), mean diuresis volume (B), congestion score index (C), and delta weight reduction (D) between the frusemide and metolazone groups.

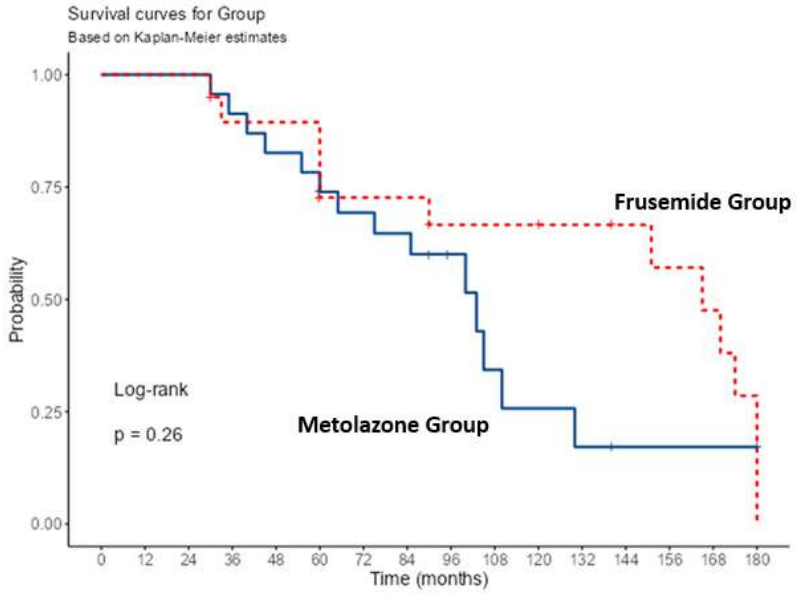

Fig. (2): kaplan Meier Curve for survival over 180 days.

4. Discussion

Loop diuretics remain the cornerstone and first-line therapy for the management of congestion in patients with acute decompensated heart failure. However, in patients with chronic heart failure receiving long-term loop diuretic therapy, diuretic resistance frequently develops, leading to a diminished natriuretic and diuretic response. This often necessitates progressive escalation of loop diuretic doses, which is associated with an increased risk of adverse effects, including worsening renal function,

electrolyte disturbances, and neurohormonal activation.

The sequential nephron blockade, achieved by the addition of a thiazide-like diuretic such as metolazone to loop diuretic therapy, augments natriuresis by inhibiting distal tubular sodium reabsorption and represents an effective strategy to overcome loop diuretic resistance in patients with acute decompensated heart failure (ADHF). With benefits of lowering the loop diuretics doses used.

In this study, the addition of metolazone to loop diuretic therapy was associated with a significantly improved diuretic efficiency (958.00 ± 156.46 mL/40 mg Frusemide vs, 614.35 ± 281.66 mL/40 mg; $p < 0.05$) and more effective decongestion (1.15 ± 0.37 vs 0.74 ± 0.54; $p < 0.05$) compared with Frusemide alone in patients with advanced heart failure. This aligns with prior studies indicating that sequential nephron blockade, using a thiazide-like diuretic such as metolazone in combination with a loop diuretic, enhances overall natriuresis and can overcome loop diuretic resistance in acute decompensated heart failure (ADHF) settings.(14-16)

Severe pulmonary congestion, whether quantified by CXR or lung ultrasound at admission, was associated with elevated pulmonary artery systolic pressure, supporting the mechanistic plausibility of CSI as a marker of hemodynamic burden.(13, 17-19)

The diagnostic value of chest radiography (CXR) demonstrated higher diagnostic performance for acute heart failure (AHF) was studied in previous studies (12, 20-22). CSI have a consistent diagnostic performance across age, BMI, and coexisting pulmonary conditions. The only factor that appeared to reduce CSI's diagnostic accuracy was cardiomegaly, likely due to overlap between the cardiac silhouette and relevant lung fields.(12)

In line with previous studies (13, 23), patients with more severe pulmonary congestion in our study were predominantly elderly, had higher BMI, a greater burden of cardiovascular risk factors and comorbidities, more severe congestion, impaired renal function, and elevated inflammatory markers.

Despite the recommended use of natriuretic peptides for the diagnosis of acute heart failure (AHF)(24), and their value for ruling out non-heart failure causes of acute dyspnea(24, 25), comorbidities such as advanced age and renal dysfunction may limit their diagnostic utility in a substantial proportion of patients (26, 27).

Clinical scores such as the Brest score showed a good diagnostic accuracy for heart failure (28). However, a lot of dyspneic patients lies in the intermediate "grey zone" highlighting the limitations of clinical scoring alone and the need for complementary diagnostic strategies.(29)

Additionally, BNP measurement requires time and may not be readily available in all clinical settings, compared to feasible and scalable CXR. Even in cases where the clinical diagnosis of AHF is clear, guidelines recommend prompt initiation of therapy rather than waiting for natriuretic peptide results(1, 30).

Kobayashi et al.(13) demonstrated that the Congestion Score Index (CSI) improves reclassification of acute heart failure (AHF) diagnosis beyond the Brest score and BNP. The combination of CSI and the Brest score yielded an AUC of 0.81, comparable to the combination of BNP and the Brest score (AUC 0.82).

Our study showed improved decongestion reflected by a more substantial reduction in CSI at discharge. Effective decongestion is clinically important because persistent congestion at discharge is associated with higher readmission rates and adverse outcomes in heart failure (31).

Notably, patients treated with metolazone demonstrated greater reductions in weight (−5.96 ± 2.20 kg vs, −3.65 ± 1.38 kg; $p < 0.05$) and congestion score (0.74 ± 0.54 vs.,1.15 ± 0.37; $p < 0.05$). That finding is consistent with larger retrospective analyses where metolazone addition improved congestion metrics and urine output without a significant increase in adverse events when carefully monitored.(32-34).

Another important finding was the significantly lower loop diuretic dose required at discharge in the metolazone group (155.00 ± 59.16 mg vs, 252.39 ± 137.05 mg; $p < 0.05$). These findings are consistent with the results of a recent systematic review and meta-analysis by Shrestha et al.,(35) which demonstrated that adjunctive metolazone in diuretic-resistant acute decompensated heart failure significantly improved diuretic response and net fluid removal when compared with loop diuretics alone. Improved natriuresis and volume control may facilitate earlier stabilization and enable clinicians to down-titrate loop diuretic doses prior to discharge, potentially mitigating the adverse neurohormonal activation and renal dysfunction associated with high-dose loop diuretic exposure. Collectively, these data support the role of metolazone as an effective loop-diuretic–sparing strategy in carefully selected patients with diuretic resistance.

In the present study, Kaplan–Meier survival analysis demonstrated a numerically longer mean survival time in patients treated with metolazone compared with those receiving Frusemide alone. Although the observed difference favored the metolazone group, it did not reach statistical

significance (SE 11.0; 95% CI 78.2–121.4 vs, SE 13.8; 95% CI 105.9–160.1; P = 0.37).

This finding suggests that while sequential nephron blockade may be associated with a trend toward improved long-term outcomes, the survival benefit could not be conclusively demonstrated within the current cohort.

The absence of statistical significance may be attributed to survival in patients with advanced heart failure is influenced by multiple competing factors, such as baseline disease severity, comorbid conditions, renal function, and adherence to guideline-directed medical therapy, which may attenuate the independent effect of diuretic strategy on long-term survival. Importantly, diuretics primarily serve a symptomatic and decongestive role rather than directly modifying disease progression, which may explain why improvements in congestion and diuretic efficiency do not necessarily translate into a measurable survival advantage.(36)

Nevertheless, the numerically longer survival observed in the metolazone group is clinically noteworthy and consistent with the hypothesis that more effective and sustained decongestion, achieved through sequential nephron blockade, may indirectly influence prognosis by reducing residual congestion, rehospitalization, and neurohormonal activation associated with high-dose loop diuretic exposure. Persistent congestion and diuretic resistance have been consistently identified as strong predictors of adverse outcomes in heart failure, including increased mortality and readmission rates, supporting the biological plausibility of this observed trend.(37)

Study Limitations

Several limitations should be acknowledged. First, this was a single-center, retrospective observational study, which inherently limits causal inference and is subject to selection bias and unmeasured confounding. Second, the relatively small sample size reduced statistical power, particularly for survival and rehospitalization outcomes, and may have contributed to the lack of statistically significant differences in long-term prognosis. Third, the decision to initiate metolazone was at the discretion of the treating physician, introducing potential treatment selection bias. Fourth, radiographic assessment of congestion, although standardized using the congestion score index, may be influenced by interobserver variability and technical limitations such as cardiomegaly or pleural effusion. Finally, follow-up data were limited to short- and mid-term outcomes, precluding definitive conclusions regarding long-term mortality or disease-modifying effects.

Conclusion

In patients with advanced ADHF, adjunctive metolazone therapy was associated with improved diuretic efficiency, more effective radiographic and clinical decongestion, and lower loop diuretic requirements at discharge, without compromising renal safety. While no statistically significant survival benefit was demonstrated, the observed trend toward improved outcomes underscores the clinical importance of achieving effective decongestion. Sequential nephron blockade with metolazone represents a valuable therapeutic option for managing diuretic resistance in selected patients with ADHF. Prospective, adequately powered randomized trials are warranted to further define its impact on long-term clinical outcomes and safety.

References

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. European heart journal. 2021;42(36):3599-726.
2. Asakage A, Mebazaa A, Deniau B. New insights in acute heart failure. Presse medicale (Paris, France : 1983). 2024;53(1):104184.
3. Cuthbert JJ, Cleland J, Pellicori P, Clark AL. Point: Natriuresis Guided Diuresis in Patients Admitted to Hospital With Heart Failure - Barking up the Wrong Tree. Journal of cardiac failure. 2025;31(2):465-8.
4. Lo KB, Nohria A. Diuretic strategies in acute decompensated heart failure. Heart failure reviews. 2025;30(2):417-30.
5. Marques P, Blydt-Hansen M, Takano T, Ferreira JP, Tsoukas MA, Sharma A, et al. Systematic Review on the Management of Diuretic Resistance in Acute Heart Failure across the Spectrum of Kidney Disease. Cardiorenal medicine. 2025;15(1):462-83.
6. Mocan D, Lala RI, Puschita M, Pilat L, Darabantiu DA, Pop-Moldovan A. The Congestion "Pandemic" in Acute Heart Failure Patients. Biomedicines. 2024;12(5).
7. Prata AA, Prata AA, Coan ACC, Scardini PG, Fernandes JM, Neto WF, et al. Protocolized natriuresis-guided diuretic therapy in acute heart failure: a systematic review and meta-analysis. Critical care (London, England). 2025;29(1):474.
8. George J, Wilson Tang WH. Evolving Decongestion Strategies in the Management of Acute Heart Failure. Current treatment options in cardiovascular medicine. 2025;27(1):71.
9. Mocan D, Lala RI, Puschita M, Pilat L, Darabantiu DA, Pop-Moldovan A. The

Congestion “Pandemic” in Acute Heart Failure Patients. 2024;12(5):951.
10. Beghini A, Sammartino AM, Papp Z, von Haehling S, Biegus J, Ponikowski P, et al. 2024 update in heart failure. ESC heart failure. 2025;12(1):8-42.
11. Kobayashi M, Watanabe M, Coiro S, Bercker M, Paku Y, Iwasaki Y, et al. Mid-term prognostic impact of residual pulmonary congestion assessed by radiographic scoring in patients admitted for worsening heart failure. International Journal of Cardiology. 2019;289:91-8.
12. Kobayashi M, Douair A, Duarte K, Jaeger D, Giacomin G, Bassand A, et al. Diagnostic performance of congestion score index evaluated from chest radiography for acute heart failure in the emergency department: A retrospective analysis from the PARADISE cohort. PLoS medicine. 2020;17(11):e1003419.
13. Kobayashi M, Bercker M, Huttin O, Pierre S, Sadoul N, Bozec E, et al. Chest X-ray quantification of admission lung congestion as a prognostic factor in patients admitted for worsening heart failure from the ICALOR cohort study. International Journal of Cardiology. 2020;299:192-8.
14. Cox ZL, Hung R, Lenihan DJ, Testani JM. Diuretic Strategies for Loop Diuretic Resistance in Acute Heart Failure: The 3T Trial. JACC Heart failure. 2020;8(3):157-68.
15. Bessa R, Martins OC, Mamede I, Franchini AEO, Santos MCF. Efficacy and safety of combining a thiazide diuretic with a loop diuretic in decompensated heart failure: A systematic review and meta-analysis. International journal of cardiology Heart & vasculature. 2025;59:101739.
16. Tran P, Khweir L, Kuehl M, Joshi M, Appunu K, Ayub W, et al. A Pragmatic Approach to Acute Cardiorenal Syndrome: Diagnostic Strategies and Targeted Therapies to Overcome Diuretic Resistance. Journal of clinical medicine. 2025;14(9).
17. Coiro S, Porot G, Rossignol P, Ambrosio G, Carluccio E, Tritto I, et al. Prognostic value of pulmonary congestion assessed by lung ultrasound imaging during heart failure hospitalisation: A two-centre cohort study. Scientific Reports. 2016;6(1):39426.
18. Platz E, Systrom D, Leopold JA. Pulmonary congestion in patients with pulmonary arterial hypertension? New insights from lung ultrasound. 2024;26(4):825-8.
19. Ltaief Z, Yerly P, Liaudet L. Pulmonary Hypertension in Left Heart Diseases: Pathophysiology, Hemodynamic Assessment and Therapeutic Management. International journal of molecular sciences. 2023;24(12).
20. Maw AM, Hassanin A, Ho PM, McInnes MDF, Moss A, Juarez-Colunga E, et al. Diagnostic Accuracy of Point-of-Care Lung Ultrasonography and Chest Radiography in Adults With Symptoms Suggestive of Acute Decompensated Heart Failure: A Systematic Review and Meta-analysis. JAMA Network Open. 2019;2(3):e190703-e.
21. Mueller-Lenke N, Rudez J, Staub D, Laule-Kilian K, Klima T, Perruchoud AP, et al. Use of chest radiography in the emergency diagnosis of acute congestive heart failure. 2006;92(5):695-6.
22. Sartini S, Frizzi J, Borselli M, Sarcoli E, Granai C, Gialli V, et al. Which method is best for an early accurate diagnosis of acute heart failure? Comparison between lung ultrasound, chest X-ray and NT pro-BNP performance: a prospective study. Internal and Emergency Medicine. 2017;12(6):861-9.
23. Platz E, Lewis EF, Uno H, Peck J, Pivetta E, Merz AA, et al. Detection and prognostic value of pulmonary congestion by lung ultrasound in ambulatory heart failure patients†. European heart journal. 2016;37(15):1244-51.
24. Çelik A, Öztürk GZ, Çavuşoğlu Y, Ardıç C, Nalbantgil S, Arıca S, et al. Guideline for the Use of Natriuretic Peptides in the Early Diagnosis and Management of Heart Failure in Primary Care (Joint Consensus Report by the Eurasian Society of Heart Failure and the Turkish Association of Family Medicine). Balkan medical journal. 2025;42(2):94-107.
25. Belkin M, Wussler D, Lopez-Ayala P, Nowak A, Gualandro DM, Sailova D, et al. A Novel N-Terminal Pro-B-Type Natriuretic Peptide Assay in the Early Diagnosis of Acute Heart Failure. 2025;4(11_Part_1):102206.
26. Neuen BL, Vaduganathan M, Claggett BL, Beldhuis I, Myhre P, Desai AS, et al. Natriuretic Peptides, Kidney Function, and Clinical Outcomes in Heart Failure With Preserved Ejection Fraction. JACC: Heart Failure. 2025;13(1):28-39.
27. Hood CJ, Gupta A, Hendren NS, Farr MA, Drazner MH, Tang WHW, et al. Influence of Age on the Impact of a Natriuretic Peptide–Guided Treatment Strategy in Patients With Heart Failure. American Journal of Cardiology. 2025;234:60-2.

28. Basset A, Nowak E, Castellant P, Gut-Gobert C, Le Gal G, L'Her E. Development of a clinical prediction score for congestive heart failure diagnosis in the emergency care setting: The Brest score. The American Journal of Emergency Medicine. 2016;34(12):2277-83.
29. Chouihed T, Bassand A, Duarte K, Jaeger D, Roth Y, Giacomin G, et al. Head-to-head comparison of diagnostic scores for acute heart failure in the emergency department: results from the PARADISE cohort. 2021.
30. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. 2022;145(18):e895-e1032.
31. Cooper L, DeVore A, Cowger J, Pinney S, Baran D, DeWald TA, et al. Patients hospitalized with acute heart failure, worsening renal function, and persistent congestion are at high risk for adverse outcomes despite current medical therapy. Clinical cardiology. 2023;46(10):1163-72.
32. Palazzuoli A, Ruocco G, Severino P, Gennari L, Pirrotta F, Stefanini A, et al. Effects of Metolazone Administration on Congestion, Diuretic Response and Renal Function in Patients with Advanced Heart Failure. Journal of clinical medicine. 2021;10(18).
33. Abbo AR, Gruber A, Volis I, Aronson D, Girerd N, Lund Kristensen S, et al. Diuresis Efficacy in Ambulatory Congested Heart Failure Patients: Intrapatient Comparison of 3 Diuretic Regimens (DEA-HF). JACC Heart failure. 2024;12(8):1396-405.
34. Tunuguntla MN, Chanti P, Nelogal SS, Maddala M, Polinati D, Lnu R, et al. A Systematic Review of Baseline Characteristics of Patients With Successful Decongestion on Combination Diuretic Therapy in Acute Decompensated Heart Failure (ADHF). Cureus. 2024;16(12):e76697.
35. Shrestha DB, Sedhai YR, Gaire S, Aryal BB, Singh K, Waheed I, et al. Use of metolazone as an adjunct therapy to loop diuretics in diuretic resistant acute decompensation of heart failure: A systematic review and meta-analysis. Health Sciences Review. 2023;7:100094.
36. Nassar G, Jameson R. Diuretic Use in Heart Failure. Reviews in cardiovascular medicine. 2025;26(10):39547.
37. Kristjánsdóttir I, Thorvaldsen T, Lund LH. Congestion and Diuretic Resistance in Acute or Worsening Heart Failure. Cardiac failure review. 2020;6:e25.