Prognostic Significance of Discharge Hyponatremia in Heart Failure Patients With Normal Admission Sodium (from the ESCAPE Trial)

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abstract

Hyponatremia in acute decompensated heart failure (HF) is indicative of a poor prognosis and predicts morbidity and mortality. We explored the predictive utility of hyponatremia at the time of hospital discharge among HF patients with normal admission sodium (Na). Characteristics and outcomes of HF patients enrolled in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness trial, who had normal Na on admission, were compared between those who were hyponatremic (Na <135 meq/L) or normonatremic on discharge.

background

Hyponatremia, defined as serum sodium (Na) <135 meq/L, is the most prevalent electrolyte abnormality in hospitalized patients.[1] Hyponatremia is especially common in patients hospitalized with acute decompensated heart failure (HF),

Present in approximately 15 to 25 % of such patients on hospital admission which has dilutional cause, mainly because of free water retention related to enhanced arginin vasopressin secretion rather than Na depletion. In contrast

hyponatremia that develops during hospitalization in HF subjects with normal admission Na is likely multifactorial because of diuretic therapy, worsening hemodynamics, and heightened neurohormonal activation or increased intake of free water. Admission hyponatremia is an important risk factor for prolonged hospital stay and higher rates of rehospitalization, in addition to short- and long-term mortality. Also, persistent hyponatremia during hospitalization and decreasing Na level after discharge have been associated with higher mortality. There is scant data in the literature examining the prognostic significance of hyponatremia on discharge in patients with normal admission Na.

methods

This study is a retrospective analysis of a limited access dataset from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial provided by the National Heart, Lung and Blood Institute.

ESCAPE was a multicenter trial involving 433 patients hospitalized with acute decompensated HF

Objectif of the study

The main objective of the present analysis is to study the prognostic significance, for various outcomes (including 6-month mortality and rehospitalization), of discharge hyponatremia in patients hospitalized with acute decompensated HF with EF $\leq$30%.

A secondary study objective is to compare post-discharge morbidity and mortality in patients with hyponatremia on discharge who had either normal or low Na on admission. Morbidity and mortality in the latter analysis was determined using the composite end point of death, cardiac rehospitalization, and cardiac transplant.

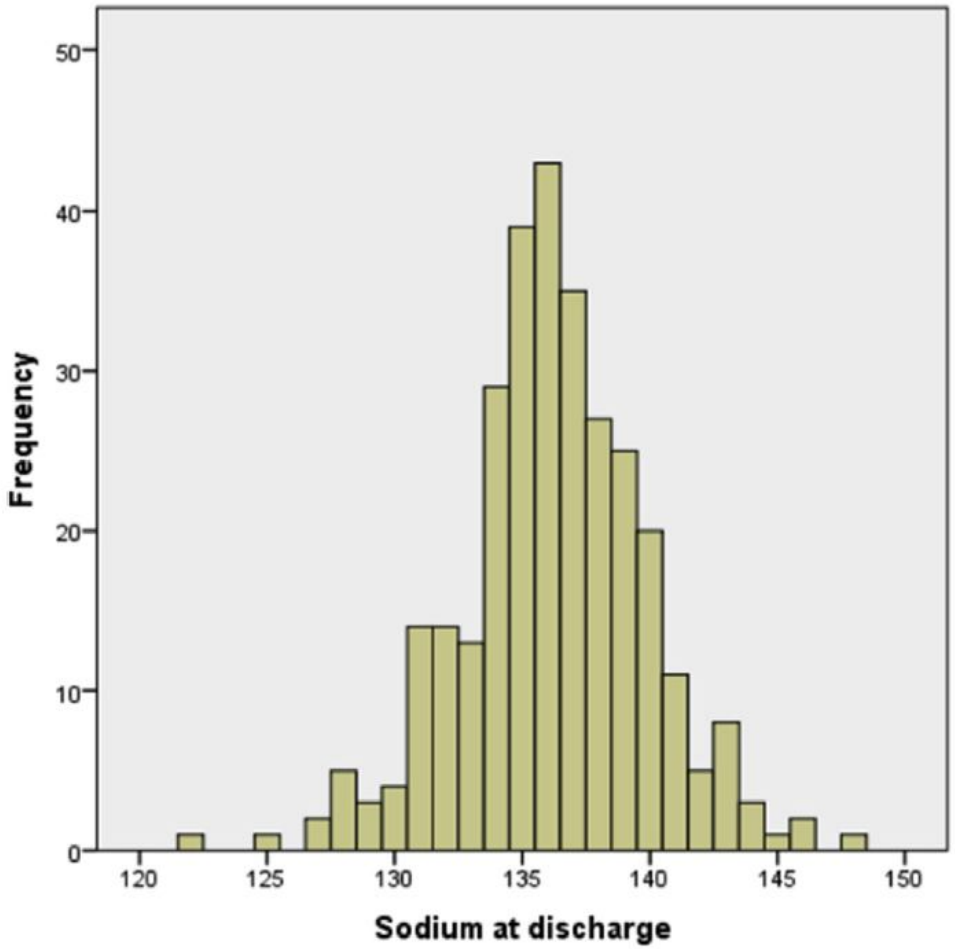

Figure 1. Distribution of serum sodium concentration on discharge among ESCAPE trial patients hospitalized with acute decompensated heart failure who were normonatremic on admission (n = 306).

Table 1
Demographics, clinical, laboratory, hemodynamic, and echocardiographic characteristics of ESCAPE trial patients with normal admission sodium and either discharge hyponatremia or normonatremia

Variable	Discharge normonatremia (n=220)	Discharge hyponatremia (n=86)	P-value
Baseline demographics			
Age (years, median, IQR)	58 (49.3, 68.8)	54.5 (44, 60)	0.004
Men	74.1% (163/220)	67.4% (58/86)	0.243
White	61.4% (135/220)	57% (49/86)	0.481
Black	25.9% (57/220)	27.9% (24/86)	0.722
BMI on admission (Kg/m^2, median, IQR)	28.1 (24.4, 33.1)	26.7 (23.3, 32.3)	0.086
Comorbidities			
Ischemic etiology of HF	49.5% (108/218)	45.3% (39/86)	0.510
Idiopathic etiology of HF	34.9% (76/218)	36% (31/86)	0.846
Atrial fibrillation	31.2% (68/218)	26.7% (23/86)	0.446
CABG	31.2% (68/218)	27.9% (24/86)	0.574
Stroke	11.5% (25/218)	4.7% (4/86)	0.068
Hypertension	54.6% (119/218)	38.4% (33/86)	0.011
DM on insulin	16.5% (36/218)	19.8% (17/86)	0.501
Malignancy	7.3% (16/218)	5.8% (5/86)	0.637
COPD	19.3% (42/218)	12.8% (11/86)	0.180
Depression	22.9% (50/218)	16.3% (14/86)	0.200
Physical exam on admission			
S3 gallop	62.8% (137/218)	78.8% (67/85)	0.008
Peripheral edema	65.1% (142/218)	70.6% (60/85)	0.366
JVD	90.2% (193/214)	95.2% (79/83)	0.164
Hepatojugular reflux	78.7% (166/211)	80% (68/85)	0.800
SBP (mmHg, median, IQR)	109 (96, 120)	101 (94, 116)	0.055
DBP (mmHg, median, IQR)	68 (60, 75)	66 (60, 71)	0.172
SBP on discharge (mmHg, median, IQR)	101 (92, 112)	94 (87, 108)	<0.001
DBP on discharge (mmHg, median, IQR)	61 (56, 70)	58 (50, 66)	0.004
Laboratory variables on admission			
BNP (pg/mL, median, IQR)	556 (245, 1130)	631 (213, 1503)	0.395
BUN (mg/dL, median, IQR)	26 (19, 38)	26.5 (18, 38.3)	0.808
Creatinine (mg/dL, median, IQR)	1.4 (1.1, 1.8)	1.25 (1, 1.7)	0.110
Total bilirubin (mg/dL, median, IQR)	0.7 (0.5, 1.2)	0.8 (0.4, 1.3)	0.919
Na (meq/L, median, IQR)	139 (137, 141)	137 (136, 139)	<0.001
Hct (%, median, IQR)	38.1 (34.2, 40.6)	37.7 (34.2, 41.4)	0.986
Laboratory variables on discharge			
BNP (pg/mL, median, IQR)	356 (150, 770)	361 (131, 1084)	0.488
BUN (mg/dL, median, IQR)	29 (19.5, 44.3)	35 (24, 58)	0.011
Creatinine (mg/dL, median, IQR)	1.4 (1.1, 1.9)	1.4 (1.05, 1.8)	0.566
Total bilirubin (mg/dL, median, IQR)	0.8 (0.5, 1.1)	0.9 (0.6, 1.35)	0.179
Na at discharge (meq/L, median, IQR)	137 (136, 139)	132 (131, 134)	<0.001
Na at optimal hemodynamic day* (meq/L, median, IQR)	138 (136, 141)	135 (131, 136)	0.001
Hct (%, median, IQR)	38 (33.1, 42.3)	36.8 (33.5, 42.2)	0.777
Echocardiographic data on admission			
EF (%, median, IQR)	20 (12, 30)	17 (13, 22)	0.074
LVEDD (median, IQR)	6.5 (5.8, 7.2)	6.6 (5.9, 7.1)	0.679
LVESD (mm, m ± SD)	5.74 ± 1.16	5.97 ± 1.08	0.186
E/A ratio (median, IQR)	2.4 (1.5, 3.4)	2.5 (1.7, 3.5)	0.493
Deceleration of E velocity (cm/sec^2, median, IQR)	132 (105, 180)	129 (110, 148)	0.362
IVC inspiration (cm, median, IQR)	1.67 (1.1, 2.2)	1.8 (1.3, 2.2)	0.491
IVC expiration (cm, mean ± SD)	2.21 ± 0.61	2.22 ± 0.60	0.984
Echocardiographic data on discharge			
EF (%, median, IQR)	22.7 (15.5, 27.9)	16.8 (13.5, 21.8)	0.007
LVEDD (mm, m ± SD)	6.50 ± 1.05	6.89 ± 1.08	0.028
LVESD (mm, median, IQR)	5.64 (5, 6.4)	6.1 (5.59, 6.55)	0.007
MR color area (mm, median, IQR)	6.3 (3.5, 11.2)	7.9 (5.3, 15.2)	0.027
Mitral annulus diameter (mL, m ± SD)	3.21 ± 0.53	3.19 ± 0.48	0.807
E/A ratio (median, IQR)	1.7 (1.1, 3.1)	2.2 (1.3, 3.4)	0.413
Deceleration of E velocity (cm/sec, median, IQR)	145 (119, 182)	122 (97, 164)	0.007
RV area during systole (cm^2, median, IQR)	18.3 (12.8, 22.5)	18.5 (13.7, 22.3)	0.997
RV area during diastole (cm^2, median, IQR)	24.5 (20.5, 29.8)	24.3 (18.8, 28.7)	0.561

Variable	Discharge normonatremia (n=220)	Discharge hyponatremia (n=86)	P-value
TR velocity (m/s, mean ± SD)	2.98 ± 0.49	2.93 ± 0.53	0.597
IVC inspiration (cm, median, IQR)	1.02 (0.53, 1.94)	1.37 (0.51, 1.96)	0.677
IVC expiration (cm, mean ± SD)	1.94 ± 0.65	1.83 ± 0.78	0.367
PAC values on admission			
RAP (mmHg, median, IQR)	12 (6.3, 15.8)	10 (6, 20)	0.924
PCWP (mmHg, mean ± SD)	23.13 ± 9.48	25.74 ± 9.81	0.160
CI (L/min/m^2, median, IQR)	1.94 (1.6, 2.3)	1.9 (1.5, 2.3)	0.927
COP (L/min, median, IQR)	3.8 (2.9, 4.6)	3.4 (2.9, 4.4)	0.424
PAC values on final hemodynamic day			
RAP (mmHg, median, IQR)	8 (5, 12)	8 (3, 12)	0.598
PCWP (mmHg, median, IQR)	16 (12, 20)	16 (10.25, 20)	0.478
CI (L/min/m^2, median, IQR)	2.3 (2, 2.8)	2.4 (2, 2.7)	0.951
COP (L/min, median, IQR)	4.6 (3.7, 5.4)	4.1 (3.5, 5.2)	0.312

ALT = alanine transaminase; AST = aspartate transaminase; BMI = body mass index; BUN = blood urea nitrogen; CABG = coronary artery bypass graft; CI = cardiac index; COP = cardiac output; COPD = chronic obstructive pulmonary disease; DBP = diastolic blood pressure; DM = diabetes mellitus; EF = ejection fraction; Hb = hemoglobin; ICD = implantable cardiac defibrillator; IQR = interquartile range; LVEDD = left ventricular end-diastolic dimension; LVEDV = left ventricular end-diastolic volume; LVESD = left ventricular end-systolic dimension; LVESV = left ventricular end-systolic volume; MI = myocardial infarction; NYHA = New York Heart Association; PADP = pulmonary artery diastolic pressure; PAMP = pulmonary artery mean pressure; PASP = pulmonary artery systolic pressure; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; SBP = systolic blood pressure.

* Sodium checked at optimal hemodynamic day which is not necessarily the day of discharge.

Table 2
Longitudinal markers of decongestion in patients with normal admission sodium level with or without discharge hyponatremia

Parameters of decongestion	Discharge normonatremia (n=220)	Discharge hyponatremia (n=86)	P-value
Admission to discharge weight loss (Kg, median, IQR)	-2.21 (-4.9, -0.34)	-2.73 (-5.4, -1.1)	0.044
Admission to discharge reduction in maximum IVC diameter (cm, median, IQR) *	-0.18 (-0.4, 0.2)	-0.36 (-0.76, -0.17)	0.014
Admission to discharge reduction in RAP (mmHg, median, IQR)	-2 (-7, 1)	-2.5 (-9, 0.8)	0.527
Admission to discharge reduction in PCWP (mmHg, median, IQR)	-6 (-12, -1)	-12 (-16, -1)	0.167
Admission to discharge reduction in PASP (mmHg, median, IQR)	-7 (-15, 0)	-16 (-25, -1.5)	0.045
Admission to discharge reduction in PADP (mmHg, median, IQR)	-4.5 (-10.3, 1.3)	-8 (-15, 0)	0.056

A negative number indicates a reduction or loss; a positive number indicates an increase or gain.

IQR = interquartile range; IVC = inferior vena cava; PADP = pulmonary artery diastolic pressure; PAMP = pulmonary artery mean pressure; PASP = pulmonary artery systolic pressure; PCWP = pulmonary capillary wedge pressure.

* Number of cases who had admission to discharge reduction in maximum IVC diameter was 35 in the discharge hyponatremia group and 68 in the discharge normonatremia group.

results

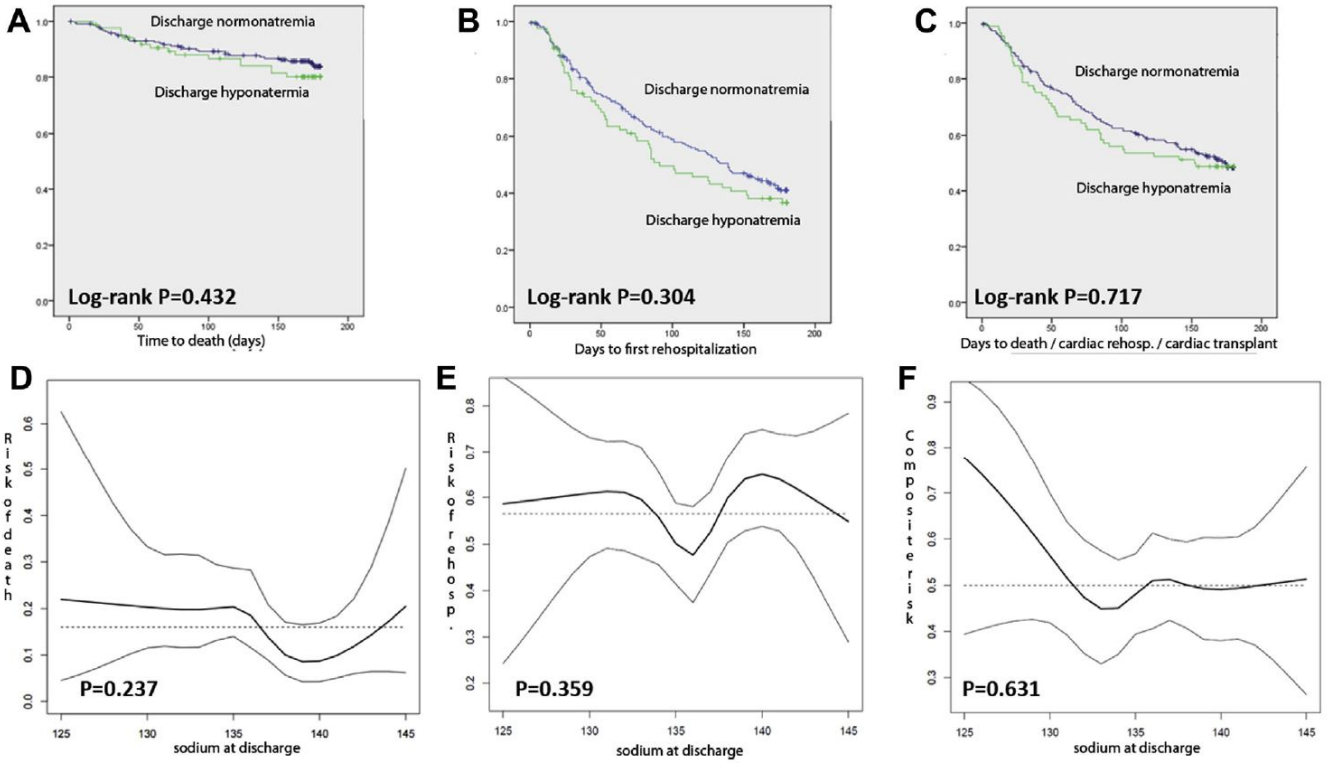

Figure 2. Kaplan-Meier curves showing no significant differences in 6-month all-cause mortality *(A)*, rehospitalization *(B)*, and composite end point of death, cardiac rehospitalization, and cardiac transplant *(C)* among patients with heart failure enrolled in the ESCAPE trial with normal admission sodium and either hyponatremia or normonatremia on discharge. *(D–F)* Restricted cubic spline fits which depict unadjusted associations between sodium at discharge and 6-month all-cause mortality, rehospitalization, and composite end point of death, cardiac rehospitalization, and cardiac transplant. The *gray curves* in *D–F* represent point-wise 95% confidence bands. The dotted horizontal lines represent the observed fractions of patients experiencing the end points. The p-values for the spline models, and that the dotted horizontal lines fit within the confidence bands, do not argue for clear associations.

Using restricted cubic splines and ordinary logistic models to examine unadjusted relation between discharge Na level and outcomes, we found no significant associations of discharge Na with all-cause mortality

Table 3
Short and intermediate-term outcomes of patients enrolled in the ESCAPE trial with or without discharge hyponatremia

Outcome	Discharge normonatremia (n=220)	Discharge hyponatremia (n=86)	P-value
Rehospitalization	55% (121/220)	60.5% (52/86)	0.386
Rehospitalization for HF	43.6% (96/220)	45.3% (39/86)	0.786
Rehospitalization for cardiac reasons	40.5% (89/220)	45.3% (39/86)	0.435
6-month mortality	15% (33/220)	18.6% (16/86)	0.440
Death during initial hospitalization or within 30d	4.1% (9/220)	2.3% (2/86)	0.476
Death due to pump failure	27.3% (9/33)	37.5% (6/16)	0.466
Patient received LVAD or cardiac transplant	7.3% (16/220)	7% (6/86)	0.959
Composite endpoint of death, rehospitalization and cardiac transplant	60.5% (133/220)	65.1% (56/86)	0.451
Composite endpoint of death, cardiac rehospitalization and cardiac transplant	49.5% (109/220)	51.2% (44/86)	0.799
Composite endpoint of death and cardiovascular rehospitalization	49.2% (32/65)	67.9% (19/28)	0.098
Number of hospitalizations (median, IQR)	2 (1, 2)	2 (1, 2.25)	0.525
Number of days of initial hospitalization (days, median, IQR)	6 (4, 9)	8 (5, 11)	0.004
Total accumulated number of days in-hospital in first 6 months (days, median, IQR)	9 (4, 21)	13 (6, 22.25)	0.045

HF = heart failure; IQR = interquartile range; LVAD = left ventricular assist device.

discussion

In line with results of a previous study by Shchekochikhin et al,[7] which is the only other study that compared patients with discharge hyponatremia and normonatremia,

the ESCAPE trial which included patients with HF and reduced EF $\leq$30%, the study by Shchekochikhin et al included patients with an International Classification of Disease diagnosis of HF irrespective of patients' systolic function. Also, their study was restricted only to in-hospital events and there was no evaluation of postdischarge outcomes, unlike the ESCAPE trial which evaluated short and intermediate-term outcomes up to 6 months after discharge. Moreover, the study by Shchekochikhin et al did not analyze patients admitted to the hospital because of acute decompensated HF

as the main admitting diagnosis but rather hospitalized patients whose discharge diagnosis code included HF. Therefore, HF may not necessarily have been the reason for admission but rather comorbidity, and hence hyponatremia may have been related to other etiologies and not necessarily to HF. The definition of hospital acquired hyponatremia in their study was hyponatremia that occurred at any time during hospitalization, so a lower Na level had not necessarily occurred at discharge. Also, Na level was adjusted for elevated serum glucose; this was not done in our study, as we did not have blood sugar values.

hyponatremia can be a marker of HF severity. HF patients with hyponatremia have higher levels of circulating catecholamines, renin, angiotensin II, aldosterone, and vasopressin compared with normonatremic patients. Moreover, hyponatremic patients have lower hepatic and renal blood flow, higher levels of transaminases, more severe renal failure, and diminished response to orthostatic

changes.[21] All these observations suggest that hyponatremia may be a marker of increased neurohormonal activation and more severe HF. Second, hyponatremia itself may directly play a pathogenic role in HF[3] and postdischarge outcomes, suggesting that Na level may be a therapeutic target. This has prompted studies to investigate the value of agents like vasopressin receptor antagonists on HF outcomes. It is also possible that the presence of hyponatremia in patients with HF will avert the use of diuretics leading to a difference in outcomes. Depletional hyponatremia related to diuretic therapy may be associated with other electrolyte abnormalities like hypokalemia and hypomagnesemia which can indirectly increase mortality.[23] Discharge hyponatremia, in our study, was not associated with postdischarge morbidity and mortality, which suggests that hyponatremia in itself is not the culprit for worse outcomes.

Study limitations & conclusion

Study limitations include its retrospective nature and the moderate sample size, which yielded wide CIs in the Cox proportional hazards regressions. Thus, although in accord with the data, a conclusion that the nature of discharge hyponatremia is benign is not definitive; in contrast, the consistency of results across analyses (i.e., for different end points, and with or without covariate adjustment) is noteworthy. The median discharge Na level in patients with discharge hyponatremia was 132 meq/L, and so our results are applicable only to mild hyponatremia on discharge.

We have not performed subgroup analysis to study the outcomes according to discharge Na level because of the modest number of cases in the discharge hyponatremia group (n = 86). Therefore, further studies are needed to study postdischarge outcomes according to the severity of hyponatremia. The ESCAPE trial limited access dataset did not have information about the dose of diuretics the patients were receiving and therefore it is hard to delineate dilutional from depletional hyponatremia. Serum glucose values were not measured in the ESCAPE trial and therefore we were unable to calculate adjusted serum Na in hyperglycemic patients. Results of this study cannot be generalized to the population of all hospitalized HF patients but rather to those with severe left ventricular systolic dysfunction and advanced symptoms.