The study included 333 patients with acute heart failure, and the authors demonstrated that higher diuretic dosing in the first 72 h of hospitalization was an independent predictor for a longer length of stay. However, we have major concerns regarding the methodology and statistical design of the study.

First, it is well known that the "length of stay" has a right skewed distribution (2, 3). Accordingly, the mean length of stay was 7.9±6.4 days, which was found to be not distributed normally [large standard deviation (SD)]. In this case, it is possible to have incorrect results if an ordinary least square (OLS) is performed for a prediction model. It is more reasonable to perform a Poisson regression or negative binomial regression analysis instead of OLS for evaluating the length of stay data. In addition, the percentage of patients was discharged from hospital is not known because a histogram for length of stay was not provided by the authors. Thus, it is not possible to extrapolate the data used for analysis regarding the percentage of patients discharged from the hospital and the diuretic dosing of the patients in the first 72 h.

Second, the authors stated that a stepwise regression model was performed by using every variable except creatinine (Cr), hematocrit (Hct), and mean arterial pressure (MAP) on presentation (there are 30 variables in Table 1). The variables were not included into the stepwise regression model because of the presence of significant multicollinearity and correlation between Cr, Hct, and MAP on presentation with blood urea nitrogen (BUN), ΔHct and ΔMAP. The major drawback for this method is to ignore the possibility that a variable and its delta or change-percent relationship can have a significant correlation. In addition, change and/or delta variables of a parameter are not considered statistically powerful compared to those obtained directly from a patient. As an example, Hct and MAP on presentation are always statistically more powerful than ΔHct and ΔMAP.

Third, it is known that the stepwise regression analysis may lead to biased and incorrect results particularly in cases of significant overfitting (4). The authors performed logistic regression analysis for 30 day readmission and in-hospital mortality. In the best scenario, there should be either 250–300 readmission and/or 250–300 in-hospital mortality outcomes to reduce the risk of overfitting (a rule of thumb at least 10). The presence of both performing stepwise regression and significant overfitting generally lead to biased/incorrect estimation of regression coefficients (as examples, diabetes mellitus reduced the risk of in-hospital mortality by 9–10 fold and brain natriuretic peptide had odds ratio=1.00, 95% confidence interval=1.00–1.00, and p=0.001 for in-hospital mortality).

Fourth, the authors performed mediation analysis to evaluate the relationship between diuretic dosing, length of stay, and worsening renal function (WRF). In fact, mediation analysis was performed by adding only one covariate to the simple regression model that included dependent and independent variables. This model had a trivial contribution to statistical analysis.

Lastly, we think it would be more appropriate to perform Poisson or negative binomial regression analysis for length of stay predictors, linear regression or quantile regression in case of violation of OLS assumption for WRF predictors, and binary logistic regression analysis for readmission and in-hospital mortality outcomes. The number of variables included in statistical models should be limited to prevent overfitting (reduce the number of candidate predictor or dimension reduction methods) or preferably use penalized regression methods. In addition, biologically plausible and other prognostically important variables should be included in the statistical models instead of choosing variables from stepwise analysis and univariable significance. The model should be improved after the imputation of missing data, and performance measures (calibration and discrimination etc.) of the model should be provided.

Göksel Çinier, İbrahim Halil Tanboğa[1]
Department of Cardiology, Kaçkar State Hospital; Rize-*Turkey*
[1]Department of Cardiology, Hisar Hospital Intercontinental; İstanbul-*Turkey*

References

1. Kato H, Fisher P, Rizk D. Higher diuretic dosing within the first 72 h is predictive of longer length of stay in patients with acute heart failure. Anatol J Cardiol 2018; 20: 110-6.
2. Andrei AC. Modeling Hospital Length of Stay Data: Pitfalls and Opportunities. Ann Thorac Surg 2016; 101: 2426.
3. Loop MS, Van Dyke MK, Chen L, Brown TM, Durant RW, Safford MM, et al. Comparison of Length of Stay, 30-Day Mortality, and 30-Day Readmission Rates in Medicare Patients With Heart Failure and With Reduced Versus Preserved Ejection Fraction. Am J Cardiol 2016; 118: 79-85.
4. Harrell FE Jr. Regression Modeling Strategies: With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis. 2nd ed. New York: Springer; 2015.

Address for Correspondence: Dr. İbrahim Halil Tanboğa,
Hisar Hospital Intercontinental,
Kardiyoloji Kliniği,
Saray Mah. Site Yolu Cad. No: 7 34768
Ümraniye/İstanbul-*Türkiye*
Phone: +90 532 163 77 21
E-mail: haliltanboga@yahoo.com

DOI:10.14744/AnatolJCardiol.2018.55948

Author`s Reply

To the Editor,

We appreciate insightful comments regarding our study demonstrating the predictive value of higher diuretic dosing in the first 72 h of hospitalization on the length of hospital stay (1). We are happy to provide further clarification and data to address their concerns in our statistical approaches.

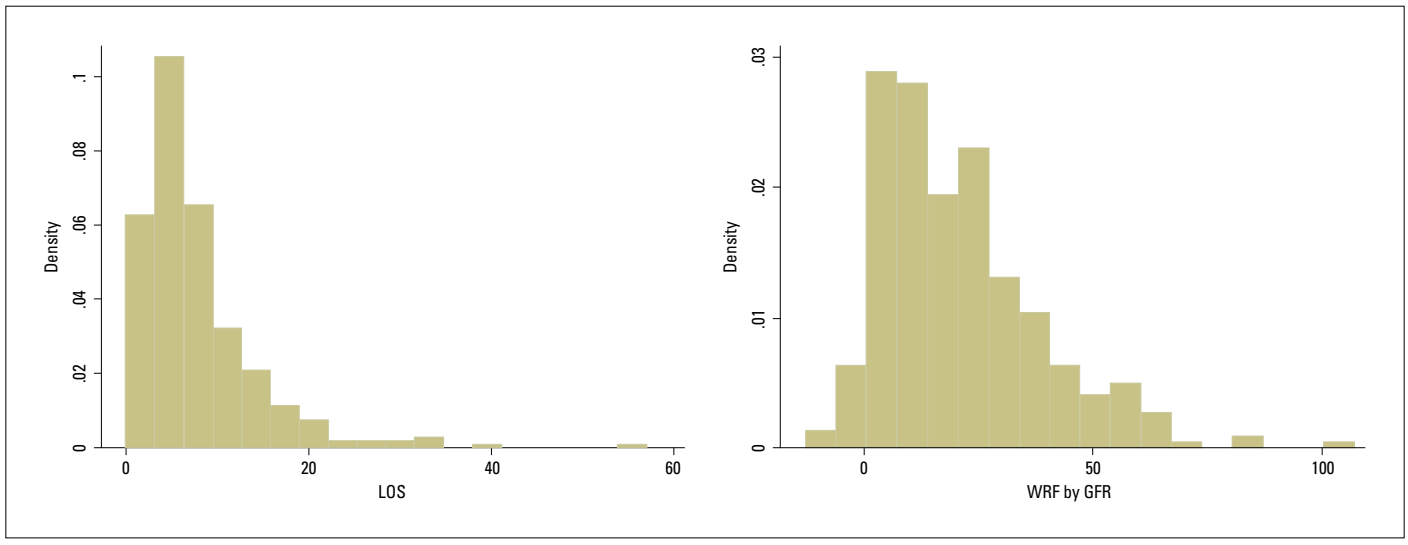

Figure 1. Distribution of LOS and WRF. The figure shows histograms of LOS (left) and WRF (right)
LOS - length of hospital stay; WRF - worsening renal failure

Table 1. Coefficients of regression models for LOS, WRF, readmission, and mortality

Variable	Coefficient	SE	Incidence rate ratio/OR	*P* value	95% CI
Length of hospital stay (Poisson regression after variable selection) (n=314)					
Total diuretic dose	0.044	0.004	1.045	<0.001	(0.036, 0.052)
EF	-0.005	0.001	0.995	<0.001	(-0.008, -0.003)
COPD	0.268	0.049	1.308	<0.001	(0.170, 0.364)
Infection	0.236	0.050	1.266	<0.001	(0.138, 0.333)
Noncompliance	-0.293	0.053	0.746	<0.001	(-0.397, -0.191)
BUN	0.004	0.001	1.004	<0.001	(0.002, 0.006)
MAP on admission	-0.006	0.001	0.994	<0.001	(-0.008, -0.003)
Worsening renal function (OLS regression with log transformation after variable selection) (n=314)					
Total diuretic dose	0.024	0.005		<0.001	(0.015, 0.034)
CKD	-0.448	0.047		<0.001	(-0.541, -0.354)
30-day readmission (Logistic regression after variable selection) (n=300)					
HF admission in 1 y	1.122	0.3016	3.070	<0.001	(0.540, 1.727)
CVA	0.932	0.3626	2.540	0.01	(0.207, 1.637)
In-hospital mortality (Firth logistic regression after variable selection) (n=314)					
EF	0.061	0.019	1.062	<0.001	(0.026, 0.102)
BUN	0.036	0.011	1.037	0.001	(0.015, 0.058)
BNP	0.001	0.0003	1.001	<0.001	(0.0005, 0.002)
MAP on admission	-0.062	0.023	0.940	0.004	(-0.113, -0.019)

For WRF, 15 points were added to each value (ΔeGFR +15) prior to log transformation because negative values were observed in cases wherein the renal function was lowest on admission then improved throughout the hospital course.
Total diuretic dose indicates the amount of diuretics in 100 mg oral furosemide equivalent administered in the first 72 h of hospitalization (1 unit is 100 mg oral furosemide equivalent). Covariates included in the Poisson and OLS regression models are total diuretic dose, age, sex, race (white or non-white), EF, history of diabetes, CKD, COPD, infection on admission, noncompliance, BUN, BNP, MAP, and angiotensin-converting enzyme inhibitor use at home. For 30-day readmission, history of CVA, HF admission in 1 year were also added. For in-hospital mortality, history of CVA, HF admission in 1 year, and aldosterone antagonist use at home was added.
EF - ejection fraction; COPD - chronic obstructive pulmonary disease; BUN - blood urea nitrogen; MAP - mean arterial pressure; CKD - chronic kidney disease; HF - heart failure; CVA - cerebrovascular accident; BNP - brain natriuretic peptide; OLS - ordinary least squares; WRF - worsening renal failure; SE - standard error; OR - odds ratio; CI - confidence interval; LOS - length of hospital stay

First, we agree that sodium and troponin levels are indeed important factors that could predict longer length of hospital stay. For this reason, we did in fact include troponin and sodium levels on admission in all statistical models as discussed in our manuscript. Both troponin and sodium levels were excluded during the stepwise selection processes, and we excluded them from Table 1 to make it more readable. Here we report that the mean sodium level (mmol/L) was 138±4.8, and the median troponin level (ng/mL) was 0.04 (0.02–0.08).

Second, we acknowledge that excluding certain predictors in the statistical model may be a limitation as mentioned in our manuscript. There is no doubt that both presence of edema on admission and change in weight during hospitalization are important predictors. However, it is well known that weights may be inaccurate or missing for a variety of reasons and that it is difficult to get true comparisons on subjective reports of edema. We would echo the challenges in retrospectively collecting accurate data for acute heart failure for particular data points due to these concerns.

Third, we are aware of the skewed distribution in length of hospital stay and WRF as shown in Figure 1. Use of OLS regression models was however advised during the study design phase since our study had enough cases. Since the concern about this statistical approach was brought to our attention, it is important to confirm whether our conclusions remain unchanged in statistical models that fit the nature of our dependent variables. To address this concern, we performed the following analyses with limited variables based on clinical importance: Poisson regression analysis for length of hospital stay, log transformed regression analysis for WRF, logistic regression analysis for readmission, and firth logistic regression analysis for in-hospital mortality. For WRF, 15 points were added to each value [Δ estimated glomerular filtration rate (ΔeGFR)+15] prior to log transformation because negative values were observed in the cases where renal function was low on admission and then improved throughout the hospital course. In addition to careful selection of clinically important covariates, we conducted further variable selection based on an exhaustive search rather than stepwise selection. The best models having the lowest Bayesian Information Criterion were selected. We present the results of those best models with variable selection in Table 1 since the statistical significance of all covariates did not change with or without variable selection. The results of models before variable selection are provided separately in Supplemental Material 1.

The statistical relationship between higher diuretic dosing and the outcomes remained unchanged. Higher diuretic dosing was predictive of longer length of hospital stay and greater reduction in eGFR but not of readmission or in-hospital mortality. The interpretation of its relationship (coefficients) however has changed. When total diuretic dose increases by 100 mg oral furosemide equivalent in the first 72 h, the length of hospital stay in days increases by 1.045 times ($e^{0.044}$=1.045) and the eGFR decreases by 2.3% of ΔeGFR+15. Predictors for longer length of hospital stay remain unchanged from the data in our manuscript. Only total diuretic dose in the first 72 h and history of chronic kidney disease remained significant in predicting WRF. Of note, we did not include change in Hct and dichotomized race into white and non-white in this analysis. Angiotensin-converting enzyme inhibitor use at home was an exception, which was no longer statistically significant in this model. For readmission, we did not observe any significant difference in results. We also agree that more cases are needed to better evaluate predictors for in-hospital mortality given its low incident rate, although we confirmed that firth logistic regression did not identify significant relationship between higher diuretic dosing and in-hospital mortality.

In conclusion, we acknowledge the study limitations in a variable selection; however, these additional analyses still favor our study findings that higher diuretic dosing in the first 72 h of hospitalization predicts inpatient outcomes including length of hospital stay and WRF.

Hirotaka Kato, Xiaoshu Li[1], Perry Fisher, Dahlia Rizk
Department of Medicine, Mount Sinai Beth Israel, Icahn School of Medicine at Mount Sinai; New York-*USA*
[1]Center for Health Services Research, University of Kentucky, Kentucky-*USA*

Reference

1. Kato H, Fisher P, Rizk D. Higher diuretic dosing within the first 72 h is predictive of longer length of stay in patients with acute heart failure. Anatol J Cardiol 2018; 20: 110-6. [CrossRef]

Address for Correspondence: Hirotaka Kato, MD,
800 Rose Street, MN 602,
Lexington KY 40536-*USA*
Phone: 414 955-0350
Fax: 414 955-0094
E-mail: hkato@uky.edu

Supplemental Material 1. Results of regression models before variable selection

Table 1. Poisson regression for length of hospital stay (n=314)

Variable	Coefficient	SE	Incidence rate ratio	*P*-value	Confidence interval
Total diuretic dose	0.044***	0.004	1.045	<0.001	(0.035, 0.052)
Age	-0.001	0.002	0.999	0.623	(-0.004, 0.002)
Sex	0.035	0.046	1.036	0.444	(-0.055, 0.125)
White	0.030	0.046	1.030	0.517	(-0.060, 0.120)
Ejection fraction	-0.005***	0.001	0.995	<0.001	(-0.007, -0.002)
Diabetes mellitus	0.019	0.043	1.019	0.662	(-0.066, 0.104)
Atrial fibrillation	0.054	0.045	1.055	0.233	(-0.034, 0.142)
Chronic kidney disease	0.028	0.046	1.028	0.544	(-0.062, 0.118)
COPD	0.283***	0.051	1.327	<0.001	(0.183, 0.383)
Infection on admission	0.235***	0.051	1.264	<0.001	(0.135, 0.334)
Noncompliance	-0.303***	0.055	0.739	<0.001	(-0.410, -0.196)
Blood urea nitrogen	0.003***	0.001	1.003	0.004	(0.001, 0.006)
BNP	0.00004*	0.00002	1.000	0.056	(0.000001, 0.0008)
MAP on admission	-0.006***	0.001	0.994	<0.001	(-0.008, -0.003)
ACEI at home	0.014	0.042	1.014	0.733	(-0.067, 0.096)
constant	2.233***	0.199	9.328	<0.001	(1.843, 2.624)

***Represents significant at 1% level; **represents significant at 5% level; *represents significant at 10% level.
COPD - chronic obstructive pulmonary disease; BNP - brain natriuretic peptide; MAP - mean arterial pressure; ACEI -angiotensin-converting enzyme inhibitor

Table 2. Log transformed regression for worsening renal function (n=314)

Variable	Coefficient	SE	*P*-value	Confidence interval
Total diuretic dose	0.023***	0.005	<0.001	(0.013, 0.034)
Age	-0.003	0.002	0.178	(-0.006, 0.001)
Sex	-0.003	0.053	0.952	(-0.107, 0.101)
White	-0.017	0.055	0.755	(-0.125, 0.090)
Ejection fraction	-0.001	0.001	0.333	(-0.004, 0.001)
Diabetes mellitus	-0.072	0.050	0.149	(-0.170, 0.026)
Atrial fibrillation	-0.065	0.052	0.213	(-0.168, 0.038)
Chronic kidney disease	-0.427***	0.054	<0.001	(-0.533, -0.320)
COPD	0.009	0.063	0.888	(-0.116, 0.134)
Infection on admission	0.042	0.063	0.506	(-0.083, 0.167)
Noncompliance	-0.075	0.060	0.217	(-0.194, 0.044)
Blood urea nitrogen	0.0005	0.002	0.757	(-0.003, 0.004)
BNP	-0.00002	0.00003	0.407	(-0.0001, 0.00003)
MAP on admission	0.0006	0.002	0.709	(-0.003, 0.004)
ACEI at home	0.057	0.049	0.241	(-0.039, 0.153)
constant	3.731***	0.225	<0.001	(3.288, 4.173)

***Represents significant at 1% level; **represents significant at 5% level; *represents significant at 10% level.
COPD - chronic obstructive pulmonary disease; BNP - brain natriuretic peptide; MAP - mean arterial pressure; ACEI -angiotensin-converting enzyme inhibitor

Table 3. Firth Logistic regression for in-hospital mortality (n=314)

Variable	Coefficient	SE	Odd ratio	*P*-value	Confidence interval
Total diuretic dose	-0.111	0.092	0.895	0.229	(-0.291, 0.070)
Age	0.017	0.034	1.017	0.621	(-0.050, 0.084)
Sex	1.056	0.792	2.875	0.182	(-0.496, 2.608)
White	0.168	0.742	1.183	0.821	(-1.286, 1.622)
Ejection fraction	0.059**	0.026	1.061	0.021	(0.009, 0.110)
Diabetes mellitus	-1.640*	0.941	0.194	0.081	(-3.484, 0.203)
Atrial fibrillation	0.610	0.790	1.840	0.440	(-0.938, 2.158)
Chronic kidney disease	-0.135	0.868	0.873	0.876	(-1.837, 1.566)
COPD	0.124	0.839	1.131	0.883	(-1.521, 1.768)
Infection on admission	-0.155	0.779	0.856	0.842	(-1.681, 1.371)
Noncompliance	-2.738	1.665	0.065	0.100	(-6.002, 0.526)
Blood urea nitrogen	0.059***	0.022	1.061	0.006	(0.017, 0.101)
BNP	0.001**	0.0004	1.001	0.001	(0.0005, 0.002)
MAP on admission	-0.027	0.026	0.973	0.298	(-0.078, 0.024)
ACEI at home	-1.692	1.077	0.184	0.116	(-3.802, 0.418)
HF admission in 1 yr	0.634	0.805	1.885	0.431	(-0.943, 2.211)
Cerebrovascular event	-1.240	1.195	0.289	0.299	(-3.581, 1.101)
AA at home	1.750	1.125	5.753	0.120	(-0.455, 3.954)
constant	-7.265	4.452	0.0007	0.103	(-15.992, 1.461)

***Represents significant at 1% level; **represents significant at 5% level; *represents significant at 10% level.
COPD - chronic obstructive pulmonary disease; BNP - brain natriuretic peptide; MAP - mean arterial pressure; ACEI -angiotensin-converting enzyme inhibitor; HF - heart failure; AA - aldosterone antagonist

Table 4. Logistic regression for 30-day readmission (n=300)

Variable	Coefficient	SE	Odd ratio	*P*-value	Confidence interval
Total diuretic dose	-0.016	0.034	0.984	0.636	(-0.082, 0.050)
Age	-0.008	0.013	0.992	0.532	(-0.034, 0.017)
Sex	-0.168	0.349	0.846	0.631	(-0.852, 0.517)
White	-0.236	0.367	0.790	0.521	(-0.956, 0.484)
Ejection fraction	-0.012	0.010	0.988	0.227	(-0.031, 0.007)
Diabetes mellitus	0.077	0.338	1.080	0.819	(-0.585, 0.739)
Atrial fibrillation	0.443	0.348	1.557	0.204	(-0.240, 1.126)
Chronic kidney disease	0.090	0.356	1.095	0.800	(-0.608, 0.788)
COPD	0.592	0.390	1.808	0.129	(-0.172, 1.356)
Infection	-0.279	0.445	0.756	0.531	(-1.152, 0.593)
Noncompliance	-0.113	0.389	0.893	0.771	(-0.876, 0.650)
Blood urea nitrogen	0.010	0.010	1.010	0.316	(-0.010, 0.030)
BNP	0.0002	0.0002	1.000	0.227	(-0.0001, 0.0005)
MAP on admission	-0.018*	0.011	0.983	0.094	(-0.038, 0.003)
ACEI at home	-0.378	0.325	0.685	0.245	(-1.015, 0.260)
HF admission in 1 yr	0.837**	0.349	2.308	0.016	(0.153, 1.520)
Cerebrovascular event	0.867**	0.401	2.381	0.030	(0.082, 1.653)
constant	0.280	1.475	1.323	0.849	(-2.611, 3.171)

Note: *** represents significant at 1% level; ** represents significant at 5% level; * represents significant at 10% level.
COPD - chronic obstructive pulmonary disease; BNP - brain natriuretic peptide; MAP - mean arterial pressure; ACEI -angiotensin-converting enzyme inhibitor; HF - heart failure