Outcomes With Ultrafiltration Among Hospitalized Patients With Acute Heart Failure (from the National Inpatient Sample)

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Acute heart failure (HF) management is a complex and often involves a delicate balance of both cardiac and renal systems. Although pharmacologic diuresis is a mainstay of the pharmacologic management of decompensated HF, ultrafiltration (UF) represents a non-pharmacologic approach in the setting of diuretic resistance. We conducted a cross-sectional analysis of the 2009 through 2014 hospitalization data from the National Inpatient Sample. The study population consisted of hospitalizations with a discharge Diagnosis Related Groups of HF who were older than 18 years of age, did not have end-stage kidney disease, acute kidney injury and had not undergone hemodialysis or hemofiltration. There were 6,174 hospitalizations which included UF among the 7,799,915 hospitalizations for HF. Hospitalizations which included UF were among patients significantly younger in age (68.1 ± 1.0 vs 73.8 ± 0.1 years), male (61.9% vs 47.7%), and with higher prevalence of co-morbid conditions including chronic kidney disease (58% vs 31%), diabetes mellitus (53% vs 42%), and higher rates of co-morbidity (Charlson comorbidity score ≥2, 92% vs 80%). All-cause mortality was significantly higher among hospitalizations which included an UF (4.68% vs 2.24%). Hospitalizations with UF had a longer mean length of stay (6.2 vs 4.3 days, p <0.01) average total charges ($42,035 vs 24,867 USD, p <0.01) as compared with those without UF. Hospitalizations with UF were associated with a greater adjusted odds of all-cause mortality (odds ratio: 3.36, [95% confidence interval 1.76,6.40]), greater than DRG-level target length of stay (odds ratio, 2.46; [95 confidence interval 1.65,3.67]), and a 72% increase in the average hospital charges. In conclusion, hospitalizations which included UF identified a subgroup of HF patients with more co-morbid conditions who are at higher risk of mortality and increased resource burden in terms of length of stay and costs. These findings also highlight that the need for UF may identify patients who are most likely to benefit from a multidisciplinary cardiorenal approach to alter the trajectory of their disease. **(Am J Cardiol 2021;142:97−102)**

Heart failure (HF) is highly prevalent and associated with frequent hospitalizations, high mortality, and cost.[1−3] The burden associated with HF is expected to continue to increase.[4] A variety of approaches have been used to reduce the hospitalization burden with HF including the use of guideline-directed medical therapies (GDMT), the application of disease management care models, and a specific focus on care transitions to reduce HF hospitalizations.[5−8] Although loop diuretics are the mainstay of medical therapy for HF with evidence of congestion, it is not uncommon that diuresis is challenged by a worsening kidney function. In fact, it is estimated that between one-third to one-half of persons with acute HF develop cardiorenal syndrome.[9] Diuretic resistance and worsening kidney function in the setting of volume overload can pose challenges and necessitate alternate means of volume removal including ultrafiltration (UF). Several studies have reported on the utility of UF on outcomes of weight loss, net fluid removal, mortality, rate of hospitalizations, and readmissions.[10−15] Systematic reviews and meta-analyses with larger sample sizes have concluded that UF is effective in both weight loss and net fluid removal without significant increase in adverse events.[16−18] However, whether UF affects the length of stay (LOS) or costs of HF hospitalizations is currently unknown. We used a large nationally representative database of inpatient HF hospitalizations to characterize HF

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hospitalization with and without ultrafiltration. In addition, we investigated the association of ultrafiltration with mortality, LOS, and costs.

Methods

We conducted a retrospective cross-sectional analysis of the observational hospital discharge data from the National Inpatient Sample (NIS) including years 2009 thru 2014. Briefly, the NIS is an annual sample of hospital discharges providing national estimates of the characteristics of patients, diagnoses, and hospital-based procedures performed in US acute-care hospitals obtained by way of the Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality.[19]

Our study's subpopulation included hospitalizations with a discharge Diagnosis Related Groups (DRG)[20] of HF (291, 292, or 293) whereas excluding persons aged younger than 18 years of age, those with a diagnosis of end-stage kidney disease, acute kidney injury (ICD-9 code: 585.6, 584, 584.5-584.9) and those on maintenance hemodialysis or hemofiltration (ICD-9 code: 39.95, V45.1, V56). The co-morbid conditions and the procedure of UF were identified using their respective *International Classification of Disease*, 9th Revision, Clinical Modification (ICD-9) codes. The Charlson index was used to account for the risk associated with co-morbid conditions.[21]

Descriptive and inferential statistics were calculated incorporating the survey design features of the NIS data in order to provide population-based estimates. Descriptive statistics were calculated for categorical and continuous variables. Survey design based linear and logistic regression was used to assess the unadjusted and adjusted association between ultrafiltration and the outcomes. Propensity scores account for any potential confounding which may be present when using observational data in the allocation of treatment were incorporated in our regression analyses.[22] Characteristics with a statistically significant association with the procedure of ultrafiltration (see Appendix) were used to calculate propensity scores. Given the complex design of the data and our study outcomes were of both continuous and binomial type we applied the propensity scores in our regression analyses based on Average Treatment Effect weighting method in order to minimize the potential bias which may have been present in the allocation of UF in hospitalized persons with HF in the assessment of its association with the outcomes of interest.[23]

For all 3 outcomes of interest, we used regression to determine the unadjusted and adjusted association with UF. The associations were assessed in 3 separate regression models. These included an unadjusted model (Model 1), a model adjusting for age, gender, chronic kidney disease (CKD) and the Charlson comorbidity score (Model 2), and a fully adjusted model which included covariates in Model 2 in addition to co-morbid conditions of coronary artery disease, hypertension, chronic obstructive pulmonary disease, diabetes mellitus, peripheral vascular disease, and cancer (Model 3).

For the outcome of hospital charges, we used survey linear regression with the dependent variable and the total charges in log-transformed form, with the regression model output reported as a percent change in hospital charges per-unit change in the independent variable. To ensure adequacy of a linear regression model, the distribution of the residual errors was assessed using a histogram plot and homoscedasticity of the residual error terms was assessed by checking the Spearman rank correlation coefficient between the absolute values of the residuals and the predicted values. A plot of observed versus predicted values was used to assess the assumption of linear association between charges and the independent variables. The LOS outcome had a heavy positively skewed distribution, and thus its analysis by linear regression was not feasible due to lack of meeting the assumptions of a linear regression in both original and transformed forms. We used a logistic regression model and dichotomized the LOS outcome based on a threshold value for LOS using the 2019 Medicare arithmetic mean LOS, with a cut-off value of 2.8 days (d) for HF DRG of 293, 4.0 d for DRG 292, and 5.2 d for DRG 291. Survey logistic regression was also used to determine the association between UF with all-cause in-hospital mortality.

A significance level of 0.05 with a 2-sided test was used for all hypotheses. Missing values in the analyses were handled as missing values completely at random. Any missing design weights were replaced with the mean weight for the subpopulation. The statistical analyses were conducted using SAS Statistical Software (SAS Corporation, Cary, North Carolina). The statistical analyses incorporated the features of the survey design in order to provide population-based estimates.

Results

Table 1 displays the characteristics of the study sample. The study sample included a total weighted frequency of 7,799,915 hospitalizations of which 6,174 were with and 7,793,741 without an UF during the hospitalization. Table 2 displays the characteristics of the study sample by UF status. The UF patients were younger (68.1 ± 1.0 years(y) vs 73.8 ± 0.1 y; p <0.01), more likely to be male, and to have CKD, diabetes mellitus, and a Charlson comorbidity score of ≥2 while less likely to have diagnoses of hypertension or cancer. Among those who underwent UF during the hospitalization, 3,603 subjects had documented, predominantly unspecified stage, CKD.

An in-hospital all-cause mortality occurred in 174,428 (2.24%) with a higher mortality among those with as compared with without UF (4.69% vs 2.24%; p = 0.0001). Hospitalizations with UF had a significantly higher adjusted odds of mortality relative to those without UF (odds ratio [OR]: 3.36, [95% confidence interval [CI], 1.76 to 6.40]).

The average LOS was longer among patients undergoing UF (6.2 vs 4.3 days; p <0.01). Overall, 47.8% of the hospitalizations had a LOS longer than targeted LOS and the proportion of hospitalizations with higher than target LOS was greater in those with as compared to without UF (69.9% vs 47.7%). Hospitalizations with UF had increased odds of higher than target LOS as compared with those without UF (OR: 2.57; [95% CI, 1.84 to 3.59]), including after adjustment for co-morbidities (OR: 2.46, [95% CI, 1.65 to 3.67]).

Table 1
Characteristic, both nonweighted and weighted by survey design features, of study sample

Variable	Study population (n = 7,799,915)	
	n±SE	%±SE
Age (Years)		
18 to 50	522,355 ± 9,126	6.7 ± 0.1
50 to 75	2,960,882 ± 34,035	38.0 ± 0.2
75 and over	4,316,678 ± 51,856	55.3 ±0.2
Female	4,080,590 ± 45,081	52.3 ± 0.1
Chronic kidney disease	2,430,703 ± 29,407	31.2 ± 0.2
Coronary artery disease	57,833 ± 1,193	0.7 ± 0.01
Hypertension	5,230,336 ± 58,371	67.1 ± 0.2
Chronic obstructive pulmonary disease	2,910,484 ± 32,899	37.3±0.1
Diabetes mellitus	3,258,641 ± 36,716	41.8 ± 0.1
Peripheral vascular disease	618,943 ± 8,478	7.9 ± 0.1
Cancer	286,854 ± 3,837	3.7 ± 0.03
Atrial fibrillation	30,478 ± 723	0.4 ± 0.01
Charlson score		
0	11,041 ± 957	0.1 ± 0.01
1	1,514,837 ± 18,118	19.4 ± 0.1
2 or Higher	6,274,038 ± 69,430	80.4 ± 0.1

n = sample size; SE, Standard Error; %, Percent.

The average total charge for the HF hospitalization in the entire study population was $24,881 which was significantly higher among those with as compared to those without UF during the hospitalization ($42,035 ± 3,512 vs 24,867 ± 227; p <0.01). In an unadjusted regression model, UF was associated with a 66.6 % increase in the average hospitalization charges. After accounting for potential confounding characteristics, the fully adjusted model revealed a 72% increase in the average hospital charges associated with hospitalizations which included an UF.

Discussion

Using a large nationally representative sample we assessed the association between UF and hospital-based outcomes of LOS, total charges, and all-cause mortality. The results of our study have several notable findings. Hospitalizations with UF included younger patients and sicker in terms of a greater proportion of patients with a higher Charlson comorbidity score category. In terms of in-hospital all-cause mortality, hospitalizations with UF were at three-fold greater odds of mortality relative to those who did not require UF. Hospitalization within which there was an UF had nearly 2.5-fold greater odds of having a longer than average hospital LOS and a 72% chance of higher than average charges. Hospitalizations with UF tended to include a higher proportion of younger patients and were more likely to include patients that were sicker in terms of a greater proportion of patients with a higher Charlson comorbidity score category.

HF is a clinical syndrome which adversely impacts lives, utilization of health care resources, and health care costs. In the decompensated state, hemodynamic and neurohormonal abnormalities perpetuate a state of volume overload along with congestion. Although loop diuresis remains the main stay of HF treatment, renal function abnormalities are relatively common. Although previous literature has noted the utility of UF on outcomes of weight loss, net fluid removal, mortality, rate of hospitalizations, and readmissions there was little known regarding its impact on charges, LOS, and in-hospital mortality. Our study adds to existing literature by filling this void.

Two randomized, controlled trials have investigated the role of UF in acute decompensated HF in hospitalized patients with and without cardiorenal syndrome.[11,12] The UNLOAD trial (Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure) was a prospective, randomized control trial comparing UF within 48-hours of randomization to intravenous diuresis among patients (n = 200) hospitalized for volume overload due to decompensated HF, with the primary end points of short-term weight loss and dyspnea rating. Dyspnea rating, which was measures based on Likert scale (1 = markedly worse to 7 = markedly better), improved in both trial arms with nonsignificant difference in the magnitude of improvement (6.4 ± 0.11 vs 6.1 ± 0.15; p = 0.35). Weight loss, which was negatively correlated with fluid loss, was noted to be significantly greater among patients treated with UF as compared with the diuretics (5.0 ± 3.1 kg vs 3.1 ± 3.5 kg, p = 0.001). The study did assess the hospitalization average LOS as a secondary end point and did not find a statistically significant difference between the UF and diuretic treatment arms (6.3 ± 4.9 days vs 5.8 ± 3.8 days; p = 0.98). Notable exclusions from the UNLOAD study population included those with a serum creatinine >3.0 or with co-morbid conditions that were expected to prolong the hospitalization. The CARESS-HF (Cardiorenal Rescue Study in Acute Decompensated Heart Failure) study aimed to compare UF to diuretic-based stepped pharmacologic in acute cardiorenal syndrome using a randomized control study design. Acute cardiorenal syndrome was defined as an increase in creatinine of at least 0.3 mg per deciliter within 12 weeks before or 10 days after the HF hospitalization while excluding patients with a serum creatinine level of more than 3.5 mg per deciliter at admission time. In this study, which had a bivariate primary end point consisting of a change in weight and serum creatinine, a total of 188 patients were randomized into 2 treatment groups of 84 subjects. This study found no significant difference in a composite end point of death or rehospitalization for HF (38% vs 35%; p = 0.96) or all-cause death or rehospitalization (61% vs 48%; p = 0.12) when comparing UF with pharmacologic treatment group. Based on the results from the CARRESS-HF there is a lack of evidence for role of early UF in type 1 cardiorenal syndrome. However, rescue UF is necessary in patients who are truly diuretic refractory. Patients who are diuretic refractory are

Table 2
Characteristics of study sample by ultraflitration status

Characteristic	Ultrafiltration				p Value
	Yes		No		
	n±SE	%±SE	n±SE	%±SE	
Age					<0.0001
18 to 50	601 ± 165	9.7 ± 1.8	521,755 ± 9,110	7.0 ± 0.1	
50 to 75	3,368 ± 539	54.6 ± 2.4	2,957,514 ± 33,982	37.9 ± 0.2	
75 and Over	2,205 ± 322	35.7 ± 3.3	4,314,473 ± 51,813	55.4 ± 0.2	
Gender					<0.0001
Female	2,353 ± 384	38.1 ± 2.0	4,078,237 ± 45,050	52.3 ± 0.1	
Chronic kidney disease					<0.0001
	3,603 ± 550	58.4 ± 2.3	2,427,100 ± 29,326	31.1 ± 0.2	
Coronary artery disease					0.92
	48 ± 22	0.8 ± 0.4	57,786 ± 1,193	0.7 ± 0.01	
Hypertension					<0.0001
	3,592 ± 547	58.2 ± 2.1	5,226,744 ± 58,315	67.1 ± 0.2	
Atrial fibrillation					0.12
	48 ± 21	0.8 ± 0.3	30,430 ± 723	0.4 ± 0.01	
Chronic obstructive pulmonary disease					0.002
	1,894 ± 329	30.7 ± 2.1	2,908,590 ± 32,871	37.3 ± 0.1	
Diabetes mellitus					<0.0001
	3,272 ± 544	53.0 ± 2.6	3,255,370 ± 36,660	41.8 ± 0.1	
Peripheral vascular disease					0.70
	520 ± 117	8.4 ± 1.3	618,423 ± 8,470	7.9 ± 0.1	
Cancer					0.003
	89 ± 30	1.4 ± 0.5	286,764 ± 3,837	3.7 ± 0.03	
Charlson score					<0.0001
0 or 1	524 ± 105	8.5 ± 1.3	1,525,353 ± 18,465	19.6 ± 0.1	
2 or Higher	5,650 ± 837	91.5 ± 1.3	6,268,387 ± 69,336	80.4 ± 0.1	

n = sample size; SE = Standard Error; % = Percent.

generally a sicker population as noted by the higher Charlson comorbidity score in our study.

Previous literature has noted that a greater number of co-morbid conditions are associated with health care resource utilization, cost, and mortality.[21,24,25] Based on the all hospitalization from the 2009 NIS data, Steiner et al reported an increase in hospital mean LOS with increasing number of chronic co-morbid conditions from 4.46 days among those with 0 to 1 co-morbid conditions to 5.42 days among those with 4 or more co-morbid conditions. In terms of mean hospital charges, there was an increase from $35,385 to $38,672 USD among those with 0 to 1 co-morbid conditions and 4 or more co-morbid conditions, respectively.[26] Additionally, co-morbidity scores have been shown useful predictor of future health care cost.[25] Therefore, given the higher prevalence of co-morbid conditions among those with UF the findings of our study should not surprising. Given that our models accounted for a number of specific co-morbid conditions along with the Charlson comorbidity index, we suspect that the presence of residual confounding. These residual confounders may be due to factors which we were unable to account for based on laboratory and/or diagnostic tests. An additional consideration is the possibility of missed or residual confounding based on factors which may have resulted from our reliance on discharge ICD codes.[27]

The main strength of our study was a consequence of the use of real-world data from a nationally representative database of acute inpatient hospitalization from across the United States.[19,28] Given its representativeness of the overall health care use, the NIS is considered an ideal database for describing primary conditions along with secondary co-morbid conditions, health care utilization, studying costs, and also studying rare diseases or procedures.[29] An additional strength of our study was the use of propensity scores to account for potential confounding in the allocation of UF.

The limitations and potential biases in studies using administration databases have been previously published.[27–29] The NIS is a database with the hospitalization discharge as the unit of observation and not the individual therefore the possibility of repeat hospitalization for a unique patient cannot be excluded. The NIS does not include diagnostic or laboratory test information, for example echocardiograms, therefore limiting the incorporation of such potential confounders into our analyses. Also, due to significant number of missing fields for the NIS day of procedure variable, we were unable to take into account for the timing of the UF procedure in the analyses for its association the outcomes of interest. Although we did use propensity scores, we could only adjust for known confounders in the allocation of ultrafiltration. As such, residual confounders, including physician-level and hospital-level factors may have remained that could have contributed to charges and LOS. Given that a significant proportion (>90%) of the patients undergoing UF had unspecified stage CKD, the possibility of advanced stage CKD which could have impacted the decision to perform UF in this population could not be excluded. Finally, we were unable to assess the association between the specific CKD stage and the outcomes due to the majority of the CKD diagnoses coded as unspecified stage CKD.

Conclusion

We found hospitalizations including an UF to be associated with longer LOS, higher charges, and increased mortality. Additionally, this subgroup of patients had a higher number of co-morbid conditions which is, in itself, a predictor of increased cost and risk of mortality. Our findings, highlight that the need for UF while hospitalized for decompensated HF could serve as an indicator of a subset of HF patients who would greatly benefit from aggressive therapies to modulate the trajectory of their HF. Given the existing gaps in adherence to GDMT among HF patients which have been previously recognized,[30,31] special attention should be directed towards this aim in this subset of HF patients. Additionally, especially in patients with reduced ejection fraction, non-pharmacologic interventions such as cardiac resynchronization therapy in addition to a multidisciplinary cardiorenal team approach to their care.

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Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.11.041.

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2. Kazi DS, Mark DB. The economics of heart failure. *Heart Fail Clin* 2013;9:93–106. https://doi.org/10.1016/j.hfc.2012.09.005.
3. Dunlay SM, Shah ND, Shi Q, Morlan B, VanHouten HHall, Long K, VL Roger. Lifetime costs of medical care after heart failure diagnosis. *Circ Cardiovasc Qual Outcomes* 2011;4:68–75. https://doi.org/10.1161/CIRCOUTCOMES.110.957225.
4. Yazdanyar A, Newman AB. The burden of cardiovascular disease in the elderly: morbidity, mortality, and costs. *Clin Geriatr Med* 2009;25:563–577.
5. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;62:e147–e239.
6. Deedwania PC, Carbajal E. Evidence-based therapy for heart failure. *Med Clin North Am* 2012;96:915–931. https://doi.org/10.1016/j.mcna.2012.07.010.
7. Davidson PM, Newton PJ, Tankumpuan T, Paull G, Dennison-Himmelfarb C. Multidisciplinary management of chronic heart failure: principles and future trends. *Clin Ther* 2015;37:2225–2233. https://doi.org/10.1016/j.clinthera.2015.08.021.
8. Cowie MR, Anker SD, Cleland JG, Felker GM, Filippatos G, Jaarsma T, Jourdain P, Knight E, Massie B, Ponikowski P, López-Sendón J. Improving care for patients with acute heart failure: before, during and after hospitalization. *ESC Heart Failure* 2014:110–145.
9. Rangaswami J, Bhalla V, Blair JE, Chang TI, Costa S, Lentine KL, Lerma EV, Mezue K, Molitch M, Mullens W, Ronco C. Cardiorenal syndrome: classification, pathophysiology, diagnosis, and treatment strategies: a scientific statement from the American Heart Association. *Circulation* 2019;139:e840–e878.
10. Bart BA, Boyle A, Bank AJ, Anand I, Olivari MT, Kraemer M, Mackedanz S, Sobotka PA, Schollmeyer M, Goldsmith SR. Ultrafiltration versus usual care for hospitalized patients with heart failure: the relief for acutely fluid-overloaded patients with decompensated congestive heart failure (RAPID-CHF) trial. *J Am Coll Cardiol* 2005;46:2043–2046.
11. Bart BA, Goldsmith SR, Lee KL, Givertz MM, O'Connor CM, Bull DA, Redfield MM, Deswal A, Rouleau JL, LeWinter MM, Ofili EO. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. *N Engl J Med* 2012;367:2296–2304.
12. Costanzo MR, Guglin ME, Saltzberg MT, Jessup ML, Bart BA, Teerlink JR, UNLOAD Trial Investigators. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J Card Fail* 2010;16:277–284.
13. Giglioli C, Landi D, Cecchi E, Chiostri M, Gensini GF, Valente S, Ciaccheri M, Castelli G, Romano SM. Effects of ULTRAfiltration vs. DIureticS on clinical, biohumoral and haemodynamic variables in patients with deCOmpensated heart failure: the ULTRADISCO study. *Eur Heart J* 2011:(3):337–346.
14. Hanna MA, Wilson Tang WH, Teo BW, O'Neill JO, Weinstein DM, Lau SM, Van Lente F, Starling RC, Paganini EP, Taylor DO. Extracorporeal ultrafiltration vs conventional diuretic therapy in advanced decompensated heart failure. *Congestive Heart Failure* 2012:54–63.
15. Marenzi G, Muratori M, Cosentino ER, Rinaldi ER, Donghi V, Milazzo V, Ferramosca E, Borghi C, Santoro A, Agostoni P. Continuous ultrafiltration for congestive heart failure: the CUORE trial. *J Cardiac Failure* 2014;20:9–17.
16. Barkoudah E, Kodali S, Okoroh J, Sethi R, Hulten E, Suemoto C, Bittencourt MS. Meta-analysis of ultrafiltration versus diuretics treatment option for overload volume reduction in patients with acute decompensated heart failure. *Arq Bras Cardiol* 2015;104(5):417–425. https://doi.org/10.5935/abc.20140212.
17. Kwong JSW, Yu C-M. Ultrafiltration for acute decompensated heart failure: a systematic review and meta-analysis of randomized controlled trials. *Int J Cardiol* 2014;172:395–402. https://doi.org/10.1016/j.ijcard.2014.01.069.
18. Wen H, Zhang Y, Zhu J, Lan Y, Yang H. Ultrafiltration versus intravenous diuretic therapy to treat acute heart failure: a systematic review. *Am J Cardiovasc Drugs Drugs Devices Interv* 2013;13:365–373. https://doi.org/10.1007/s40256-013-0034-3.

19. HCUP-US NIS Overview. Accessed June 17, 2018. https://www.hcup-us.ahrq.gov/nisoverview.jsp
20. Averill RF. The design and development of the diagnosis related groups. *Top Health Rec Manage* 1984;4:66–76.
21. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–383.
22. D'Agostino RB. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med 17:2265-2281. doi:10.1002/(SICI)1097-0258(19981015)17:19<2265::AID-SIM918>3.0.CO;2-B
23. Dugoff EH, Schuler M, Stuart EA. Generalizing observational study results: applying propensity score methods to complex surveys. *Health Serv Res* 2014;49:284–303. https://doi.org/10.1111/1475-6773.12090.
24. Sambamoorthi U, Tan X, Deb A. Multiple chronic conditions and healthcare costs among adults. *Expert Rev Pharmacoecon Outcomes Res* 2015;15:823–832. https://doi.org/10.1586/14737167.2015.1091730.
25. Charlson M, Wells MT, Ullman R, King F, Shmukler C. The Charlson comorbidity index can be used prospectively to identify patients who will incur high future costs. *PLoS ONE* 2014;9. https://doi.org/10.1371/journal.pone.0112479.
26. Steiner CA, Friedman B. Hospital utilization, costs, and mortality for adults with multiple chronic conditions, nationwide inpatient sample, 2009. *Prev Chronic Dis* 2013;10. https://doi.org/10.5888/pcd10.120292.
27. Berthelsen CL. Evaluation of coding data quality of the HCUP national inpatient sample. *Top Health Inf Manage* 2000;21:10–23.
28. Sarrazin MSV, Rosenthal GE. Finding pure and simple truths with administrative data. *JAMA* 2012;307:1433–1435. https://doi.org/10.1001/jama.2012.404.
29. Stulberg JJ, Haut ER. Practical guide to surgical data sets: healthcare cost and utilization project National Inpatient Sample (NIS). *JAMA Surg* 2018;153:586. https://doi.org/10.1001/jamasurg.2018.0542.
30. Callender T, Woodward M, Roth G, et al. Heart failure care in low- and middle-income countries: a systematic review and meta-analysis. *PLoS Med* 2014;11:e1001699. https://doi.org/10.1371/journal.pmed.1001699.
31. Nieminen MS, Brutsaert D, Dickstein K, et al. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. *Eur Heart J* 2006;27:2725–2736. https://doi.org/10.1093/eurheartj/ehl193.