Protein-Energy Malnutrition and Outcomes of Hospitalizations for Heart Failure in the USA

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Chronically elevated cytokines from un-abating low-grade inflammation in heart failure (HF) results in Protein-Energy Malnutrition (PEM). However, the impact of PEM on clinical outcomes of admissions for HF exacerbations has not been evaluated in a national data. From the 2012 to 2014 Nationwide Inpatient Sample (NIS) patient's discharge records for primary HF admissions, we identified patients with concomitant PEM, and their demographic and comorbid factors. We propensity-matched PEM cohorts (32,771) to no-PEM controls (1:1) using a greedy algorithm-based methodology and estimated the effect of different clinical outcomes (SAS 9.4). There were 32,771 (~163,885) cases of PEM among the 541,679 (~2,708,395) primary admissions for HF between 2012 and 2014 in the US. PEM cases were older (PEM:76 vs no-PEM:72 years), Whites (70.75% vs 67.30%), and had higher comorbid burden, with Deyo-comorbidity index >3 (31.61% vs 26.30%). However, PEM cases had lower rates of obesity, hyperlipidemia and diabetes. After propensity-matching, PEM was associated with higher mortality (AOR:2.48 [2.31 to 2.66]), cardiogenic shock (3.11[2.79 to 3.46]), cardiac arrest (2.30[1.96 to 2.70]), acute kidney failure (1.49[1.44 to 1.54]), acute respiratory failure (1.57[1.51 to 1.64]), mechanical ventilation (2.72[2.50 to 2.97]). PEM also resulted in higher non-routine discharges (2.24 [2.17 to 2.31]), hospital cost ($80,534[78,496 to 82,625] vs $43,226[42,376 to 44,093]) and longer duration of admission (8.6[8.5 to 8.7] vs 5.3[5.2 to 5.3] days). In conclusion, PEM is a prevailing comorbidity among hospitalized HF subjects, and results in devastating health outcomes. Early identification and prevention of PEM in HF subjects during clinic visits and prompt treatment of PEM both in the clinic and during hospitalization are essential to decrease the excess burden of PEM. **(Am J Cardiol 2019;123:929−935)**

Heart failure (HF) exacerbation is a frequent reason for hospitalization in the USA, responsible for about 398 hospitalizations per 100,000 persons in 2014 and $31 billion of health care expenses in 2012.[1,2] Hallmark features of HF are chronic neurohormonal changes, elevated sympathetic outflow, and chronic low-grade inflammation, which are further aberrant during exacerbations.[3] Although the mechanism and clinical implication of the first 2 features have been well characterized and pharmacologically targeted, the pathogenesis of the inflammation is poorly understood.[4] However, the insidious inflammation with elevated inflammatory cytokines, including TNF-alpha, triggers chronic pathological changes in the body, such as defective intestinal nutrient absorption, low body stores of proteins and energy, resulting in protein-energy malnutrition (PEM).[5] Similar to HF, PEM aggravates other clinical illnesses, and is a significant burden on the American health care system.[6] The presence of concomitant PEM which might indicate the severity of the baseline inflammation, its attendant tissue destruction is often neglected. Furthermore, individuals with concomitant HF and PEM might be more susceptible to triggers of HF exacerbation, and might have delayed recuperation from each exacerbation. Since current studies on the outcomes of PEM among HF are single centered[7] or focused only on mortality,[8] we carried out this study to measure the effect of PEM on many clinical outcomes and to report the national burden of PEM on HF hospitalizations.

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Methods

This is a retrospective cohort study on the Nationwide Inpatient Sample (NIS) database from January 1st, 2012 to December 31st, 2014. Maintained by the Agency for Healthcare Research and Quality (AHRQ), the NIS is the largest, all-payer database containing hospitalized patient data from over 4,000 nonfederal acute community hospitals in over 30 states in the US.[9] A multistaged, stratified, clustered sampling methodology was used to select every discharge record from 20% of the hospitals. Each record contains demographic and co-morbid variables, and up to 30 diagnoses and 15 procedures encoded in the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). As the HCUP-NIS is completely de-identified, our study did not require an Institutional Review Board approval.

Every adult (age > 18 years) record, with a primary diagnosis of HF, without missing inputs, was selected as the study population (Figure 1), using ICD-9-CM codes (Table S1) recommended by American College of Cardiology and American Heart Association.[10] PEM (primary predictor) was identified with ICD-9-CM codes[11–13] (Table S1), representing cachexia, kwashiorkor, marasmus, other protein-calorie malnutrition (severe, unspecified), adult failure to thrive, loss of weight, and underweight. Used by many studies, these codes have been recommended by the Academy of Nutrition and Dietetics, and the American Society for Parenteral and Enteral Nutrition. As covariates (Table 1), demographic (age, sex, race, health insurance, income, hospital region and teaching status) and co-morbid factors (summarized to Charleson-Deyo index comorbidities was computed)[14] were also identified either as variables already present in the data (demographics), or with ICD-9-CM codes from the diagnostic variables, Clinical classification software (CCS) codes from CCS variables, or from Elixhauser variables. These ICD-9-CM codes have been used by other studies in the NIS.[15–19]

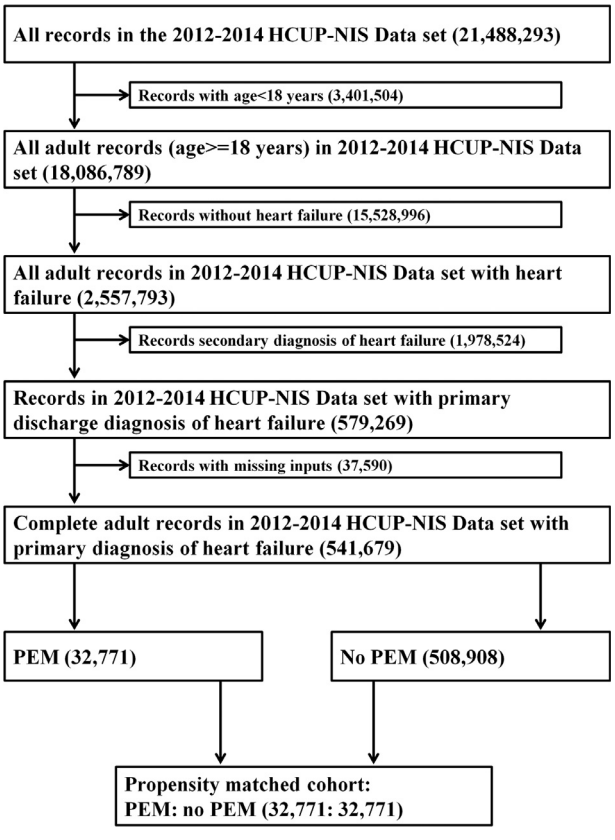

Figure 1. Selection flowchart.

Four primary (mortality, length of stay [LOS], discharge disposition, total hospital cost [THC]) and 11 secondary outcomes were studied. THC was a continuous variable, whose 2012 and 2013 values were inflated to the 2014 values to allow for even comparison. Discharge disposition, a multinomial variable, was condensed to two levels (discharge to secondary health facilities vs home). The 11 secondary outcome variables comprised of in-hospital complications of HF (shock, cardiac arrest, cerebrovascular accident, acute kidney failure [AKF], dialysis for AKF, total parenteral nutrition [TPN], transfusion, acute respiratory failure (ARF) and mechanical ventilation) and use of intra-aortic balloon pump.

All data were analyzed using Statistical Analysis System (SAS V.9.4, SAS Institute Inc, Cary, NC), accounting for the multi-staged, clustered sampling methodology as recommended by HCUP-NIS, with a p-value of <0.05 as the level of significance for statistical tests. We presented effect measures (with 95% confidence intervals [CI]) in tables and graphs with GraphPad Prism 7 (GraphPad Software, La Jolla, CA). We presented categorical variables as percentages, comparing them before and after matching with Rao-Scott Chi-square and McNemar's test respectively. Based on distribution, numerical variables were presented with mean (standard deviation, SD) or median (inter-quartile range, IQR), compared with student T-test or Mann-Whitney before matching, and with Paired T-test and Wilcoxon signed-rank test after matching. We initially compared the demographic and comorbid characteristics of PEM with no-PEM among HF subjects and developed a multivariate logistic regression to identify factors that predict the presence of PEM among the HF cohort. The model generated propensity scores, which were used to match PEM cases to no-PEM controls (1:1) using a greedy-matching algorithm,[20] with a caliper width of <0.2*SD of the logit of the propensity scores. Propensity matching is a compelling methodology that balances the covariate structure in observational studies, minimizing the size of the measured and unobserved confounding, and generally produces effect estimates similar in direction as those derived from randomized clinical control trials.[21] Many conditional regression models were designed to account for each of our 15 outcomes, with PEM as primary predictor, and the propensity score as a covariate to provide more stringent confounder adjustment. We specified distributions of these models to accommodate each outcome variable: logistic for the binary outcomes; gamma for THC; and negative binomial for LOS. The adjusted odds ratio (aOR) was reported for the logistic models and adjusted mean ratio (aMR) for the other two.

Table 1
Baseline characteristics of primary hospitalizations for heart failure by protein-energy malnutrition in the US from 2012 to 2014

		No-PEM 508,908 (∼2,544,540)	PEM 32,771 (∼163,855)	p value
Age (SD), years		72.03 (∼14.27)	76.16 (∼12.90)	<0.0001
Gender				<0.0001
	Male	50.96%	48.13%	
	Female	49.04%	51.87%	
Race				<0.0001
	Whites	67.30%	70.75%	
	Blacks	20.47%	17.09%	
	Hispanics	7.51%	6.75%	
	Others	4.72%	5.40%	
Health insurance				<0.0001
	Medicare	74.74%	81.75%	
	Medicaid	8.57%	6.05%	
	Private	11.23%	8.97%	
	Self-pay & others	5.46%	3.23%	
Household income				0.0116
	Lowest Quartile	34.05%	32.44%	
	Second Quartile	26.43%	25.90%	
	Third Quartile	21.99%	22.54%	
	Highest Quartile	17.53%	19.12%	
Hospital teaching type				<0.0001
	Rural	13.22%	10.93%	
	Urban, non-teaching	36.65%	36.40%	
	Urban, teaching	50.14%	52.67%	
Hospital region				<0.0001
	NorthEast	20.85%	17.04%	
	Midwest	21.73%	20.99%	
	South	41.63%	42.02%	
	West	15.79%	19.96%	
Deyo				<0.0001
	0	14.64%	12.46%	
	0-3	59.06%	55.94%	
	>3	26.30%	31.61%	
Peripheral vascular disease		12.65%	16.40%	<0.0001
Valvular heart disease		0.27%	0.81%	<0.0001
Hypertension		71.31%	64.40%	<0.0001
Ischemic heart disease		55.99%	54.23%	<0.0001
Cerebral vascular disease		5.36%	7.31%	<0.0001
Chronic lung disease		38.34%	37.95%	0.182
Diabetes mellitus		46.89%	36.12%	<0.0001
Chronic anemia		31.35%	43.18%	<0.0001
Coagulation disorder		5.72%	11.13%	<0.0001
Chronic liver disease		3.13%	5.00%	<0.0001
Obesity		20.99%	12.29%	<0.0001
Chronic kidney disease		44.10%	49.69%	<0.0001
Malignancies		3.49%	6.88%	<0.0001
Tobacco use		29.92%	24.93%	<0.0001
Hyperlipidemia		48.02%	39.82%	<0.0001
Acquired immune deficiency syndrome		0.18%	0.29%	<0.0001
Hyperthyroidism		0.62%	0.94%	<0.0001
Hypothyroidism		17.54%	19.88%	<0.0001
Alcohol use		3.02%	3.23%	<0.0001

Results

Among 541,679 primary HF hospitalizations, 32,771 had concomitant PEM (Figure 1 and Table 1), corresponding to 163,855 of 2,544,540 HF hospitalizations in the US with PEM, after unweighting. Patients with PEM were older (76.16 vs 72.03 years), more likely female, Whites, and to be on Medicaid health insurance PEM subjects were also more likely to reside in areas with higher income quartiles, to present to urban teaching facilities, and in the Southern and Western regions of the US. PEM patients had a higher frequency of all the comorbidities besides ischemic heart disease, diabetes mellitus, obesity, and tobacco use. Their Deyo comorbidity index (>3) was significantly higher than those without PEM (31.61% vs 26.30%).

There was some overlap in the types of malnutrition among PEM subjects, but majority had kwashiorkor/

marasmus (68.38%), followed by adult failure to thrive (19.58%), cachexia (13.33%), underweight/loss of weight (9.65%) and feeding difficulties (0.21%). All 32,771 PEM cases were successfully propensity-matched to an equal number of no-PEM controls (Figure 1 and Table S2). Matching eliminated most of the baseline differences between the two groups, and the distribution of the covariates (demographics, comorbid) became statistically identical or close. Additionally, the odds of having PEM versus no-PEM with various factors from multivariate logistic regression also became mostly non-significant after matching (Table S3).

After propensity-matching (Table 2), the frequencies of all the outcomes were higher among PEM cases compared with control. Rate of mortality was over twice higher (8.34% vs 3.55%), shock (cardiogenic and non-cardiogenic), cardiac arrest, cerebrovascular accident, AKF, hemodialysis for AKF, parenteral nutrition, blood product transfusion, acute respiratory failure, mechanical ventilation were all higher among PEM cases. Furthermore, the need for intra-aortic balloon pump, discharge to secondary health facilities, THC and LOS were higher. On conditional regression analysis, PEM cases consistently had poorer outcomes across the metrics (Table 3 and Figure 2). When contrasted to no-PEM, PEM cases had 148% higher odds of mortality, higher odds of having all types of shock, and specifically cardiogenic shock. PEM cases also had higher odds of cardiac arrest, cerebrovascular accident, AKF, and hemodialysis from the AKF. Furthermore, they had over higher odds of receiving parenteral nutrition, blood product transfusion, acute respiratory failure and need for mechanical ventilation. Additionally, PEM cases had over increased odds of needing intra-aortic balloon pump, and discharge to secondary health facilities, such as nursing homes, hospitals. Finally, PEM cases incurred 86% higher THC ($80,534[78,496 to 82,625] vs $43,226[42,376 to 44,093]) and had 63% longer hospital stay (8.6[8.5 to 8.7]- vs 5.3 [5.3 to 5.3]- days), respectively translating to approximately $37,308 excess cost and 3.3 extra days per hospitalization for HF (Table 4).

Table 3
Associations between protein-energy malnutrition and outcomes of heart failure hospitalization

	aOR	LCL	UCL	p value
Mortality	2.48	2.31	2.66	<0.0001
Shock	3.25	2.96	3.56	<0.0001
Cardiogenic shock	3.11	2.79	3.46	<0.0001
Cardiac arrest	2.30	1.96	2.70	<0.0001
Cerebrovascular accident	1.40	1.20	1.64	<0.0001
Acute kidney failure	1.49	1.44	1.54	<0.0001
Hemodialysis for acute kidney failure	2.26	2.03	2.51	<0.0001
Total parenteral nutrition	19.24	11.44	32.34	<0.0001
Transfusion	1.69	1.61	1.78	<0.0001
Acute respiratory failure	1.57	1.51	1.64	<0.0001
Mechanical ventilation	2.72	2.50	2.97	<0.0001
Balloon pump	4.13	3.22	5.30	<0.0001
Unfavorable discharge disposition	2.24	2.17	2.31	<0.0001
Total hospital cost*	1.86	1.80	1.92	<0.0001
Length of stay*	1.63	1.60	1.66	<0.0001

LCL = lower confidence limit; UCL = upper confidence limit.
* = adjusted mean ratio.

Discussion

In this study, we demonstrate that PEM is associated with dismal outcomes among patients hospitalized for HF. The rate of clinically diagnosed PEM among HF subjects in the study was higher than (6% vs 3.2%) in other studies on the entire population of hospitalized patients using a similar data.[6] This implies that HF patients have almost 2× higher rate of PEM than the general population, which is consistent with the cachexin mediated chronic inflammation induced malnutrition theory in chronic HF.[3] The ensuing

Table 2
Outcome characteristics of primary hospitalizations for heart failure by protein-energy malnutrition in the US from 2012 to 2014

	No-PEM	PEM	p value
Mortality	3.55%	8.34%	<0.0001
Shock	1.92%	5.98%	<0.0001
Cardiogenic shock	1.41%	4.25%	<0.0001
Cardiac arrest	0.65%	1.49%	<0.0001
Cerebrovascular accident	0.86%	1.21%	<0.0001
Acute kidney failure	26.55%	34.99%	<0.0001
Hemodialysis for acute kidney failure	1.48%	3.28%	<0.0001
Parenteral nutrition	0.05%	0.87%	<0.0001
Transfusion	7.84%	12.48%	<0.0001
Acute respiratory failure	12.84%	18.81%	<0.0001
Mechanical ventilation	2.19%	5.74%	<0.0001
Balloon pump counter pulsation	0.24%	0.98%	<0.0001
Unfavorable discharge disposition	30.36%	49.19%	<0.0001
Total hospital cost‡	$26,616 [14,795-46,517]	$35,290 [19,492-70,073]	<0.0001
Length of stay‡	4 [3-6] days	6 [3-10] days	<0.0001

‡ = mean cost in $US or length of stay in days.

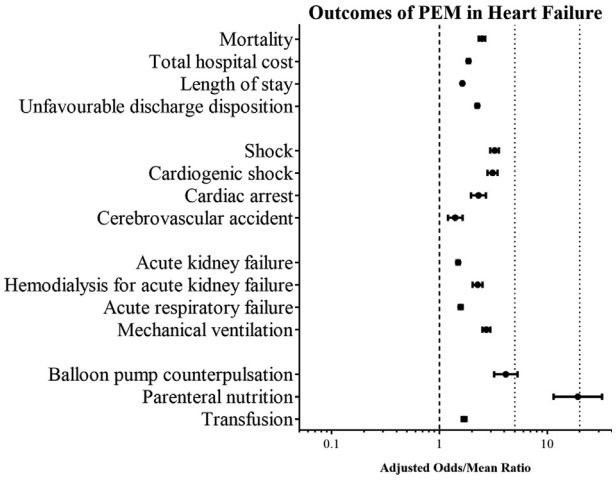

Figure 2. Effect of PEM on outcomes of primary hospitalizations for heart failure.
Effects are adjusted mean ratio (length of stay and hospital charge) and adjusted odds ratio (others).

Table 4
Adjusted mean cost and length of stay

	Total hospital cost, $			Length of stay, days		
	Mean	LCL	UCL	Mean	LCL	UCL
PEM	80534	78496	82625	8.6127	8.4887	8.7384
No PEM	43226	42376	44093	5.2809	5.2255	5.3369

LCL = lower confidence limit; UCL = upper confidence limit; * = adjusted mean ratio.

PEM is worsen by development of protein losing enteropathy in HF.[22] However, both frequencies are much lower than the numbers obtained from previous studies conducted primarily to assess PEM, which have reported a PEM frequency of about 44%, 50%, and 28% respectively among general medical, surgical and hip fracture patients.[23–25] Moreover, a recent review of many studies reports the frequency of PEM to be 20% and 50% among hospitalized patients.[26] The lower rate of PEM in studies using the NIS, such as ours, may be due to under-recognition of PEM in real-world clinical experience. Lower rates of PEM in administrative data remind us of the necessity to ensure proper documentation and ascription of ICD-9-CM codes for PEM. Under-diagnosis of PEM is concerning given that some HF subjects are volume overloaded and are likely above their baseline weight. Notably, malnutrition can occur in any weight bracket and it portends a poorer prognosis among the healthy, overweight and obese individuals.[27]

Our results of higher mortality with PEM are consistent with other studies on HF.[28,7,8] During a median 25 months follow up of 208 subjects (with 13% malnourished), a single center European study revealed a higher mortality rate with malnutrition (76% vs 18.9%).[28] Another single-center study in New York measured malnutrition with serum albumin and weight to compute a nutrition risk index (NRI), revealed a higher inpatient mortality and longer LOS among 1,740 patients.[7] Implementing a similar methodology (NRI), an American study on 160 records from 26 specialized HF centers in the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial, revealed a higher mortality rate among patients with malnutrition during the 6 months postdischarge period (38% vs 14%).[8] Our study extends these three by using a larger cohort among community hospitals caring for most US populace, across multiple centers and geographic region of the US. Unlike the hundreds of subjects used in these preceding studies, we used 541,679 records, affording more power.

Although we validate the longer LOS previously shown in other studies, we additionally reveal new associations that PEM was related to excess cost.[7] These costs might be due to the higher frequencies of complications which invariably would require more resource utilization. Higher transfer rate to secondary rehabilitation facilities on discharge for PEM patients, reflects the need for more nutritional and physical support in HF patients who may be unstable enough for routine home discharge. Well described among surgical patients,[29] we further demonstrate the higher rates of complications with PEM among HF subjects. The higher cardiovascular complications (cardiogenic shock, cardiac arrest) may reflect impaired cardiomyocyte healing capabilities from decreased nutrients.[30] Similarly, neuromuscular weakness resulting in weak respiratory efforts, and a higher rate of infection, might trigger increased respiratory and kidney complications (acute respiratory failure, AKI, and dialysis for AKI). It is reported that PEM induced muscle weakness results in higher rates of ventilation.[31] Eventually, these complications likely contributed to the higher odds of mortality among PEM subjects.

Nutrition therapy during hospitalization is commonly administered to subjects with concomitant PEM. As reported in a meta-analysis of 22 randomized clinical trials, despite broad adoption, nutrition therapy during acute illness has not consistently impacted mortality and outcomes, besides increased inpatient caloric intake, and decreased readmissions.[32] Although these studies were not specifically for HF, the data suggest that the PEM in chronic illnesses might additionally indicate the severity of their condition since acute correction did not provide inpatient mortality benefit.[32] However, continuous correction gradually replenishes the deficit, providing nutrients to facilitate healing, diminishing the ominous effect of the chronic illness, and reduces readmission rates. Therefore, early identification and prompt treatment of PEM among HF subjects in the community might provide more benefit.

Notable limitations of our study include errors in ICD-9-CM code ascription. Although the ICD-9-CM codes for HF have been rigorously validated with good accuracy,[10] those of PEM have not been scrutinized. Also, the large baseline difference in the PEM versus no-PEM group is a significant source of bias. We eliminated this bias with propensity matching, leaving some unknown residual bias, which due to pseudo-randomization from propensity-matching, likely spreads evenly across our exposure groups, resulting in a nondifferential misclassification, and deviating our estimate toward the null. Furthermore, data on the type of medications, severity, and cause of HF would have provided us insight into the possible differences in PEM and outcomes with these predictors. As the NIS lacks information after

discharge, we were unable to decipher the postdischarge outcomes, including readmissions, cost and LOS in nursing homes and rehabilitation centers. Finally, we had limited data on the severity of reduction in the ejection fraction among the HF cohorts. A lower ejection fraction might likely result in less blood and nutrient delivery to the tissues and growth impairment. If true, adjusting for ejection fraction might have eliminated such bias in our study. However, no association between NRI, an index of malnutrition and left ventricular function was found in a study.[33]

In conclusion, this study reveals the detrimental impact of PEM on inpatient outcomes of HF patients. To ensure proper follow up, studies are needed to see if implementing concomitant nutrition/dietary clinic visits at the same time as outpatient HF clinic visits might provide better treatment of any impending PEM. More importantly, a team effort of health care providers in HF clinics might facilitate early identification and treatment of PEM, to prevent the poor outcomes during hospitalizations. Furthermore, during hospitalizations, early assessment of nutrition status by nutrition experts to quickly address every underlying PEM might mitigate against these poor outcomes. Finally, more studies are needed to elucidate the mechanism of incident PEM in HF, and the optimal preventive and treatment measures.

Conflict of interest

The authors disclose no conflicts.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.amjcard.2018.12.014.

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