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ORIGINAL RESEARCH

Examining the Burden of Potentially Avoidable Heart Failure Hospitalizations

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Background: Two-thirds of the 1 million annual US CHF hospitalizations are for diuresis only; some may be avoidable. We describe a population of low-severity short-stay (</= 4 days) patients admitted for CHF.

Methods: We conducted a retrospective cohort study within the Premier Healthcare Database, 2016–2021. CHF was defined via an administrative code algorithm. High severity (CHF-H) was marked by cardiogenic shock, the need for respiratory or circulatory support, and/or a Charlson comorbidity index >2. We compared baseline characteristics, processes of care, and outcomes in low-severity (CHF-L) to CHF-H.

Results: Among 301,672 short-stay CHF patients, 135,304 (44.8%) were CHF-L. Compared to CHF-H, CHF-L was younger (70.5 ± 14.1 vs 72.1 ± 13.6 years, $p < 0.001$), more commonly female (48.6% vs 45.8%, $p < 0.001$), and more likely to receive IV ACE-I/ARB agents (0.5% vs 0.4%, $p = 0.003$). Most other IV medications were more common in CHF-H, and anticoagulation was the most prevalent non-diuretic IV therapy in both groups (23.8% vs 33.3%, $p < 0.001$). Hospital mortality (0.2% vs 1.5%, $p < 0.001$) and CHF-related 30-day readmissions (8.1% vs 10.5%, $p < 0.001$) were lower in CHF-L than CHF-H.

Conclusion: Among short-stay CHF patients, nearly ½ meet criteria for CHF-L, and are mainly admitted for fluid management. Avoiding these admissions could result in substantial savings.

Keywords: congestive heart failure, epidemiology, outcomes, hospital, costs

Introduction

Congestive heart failure (CHF) remains a frequent cause of hospitalization. According to the Agency for Healthcare Research and Quality's (AHRQ) Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample (NIS) database, in the year 2018 alone, there were nearly 5 ½ million discharges with CHF in the US. One-fifth of these were specifically for the management of heart failure as the principal reason for hospitalization. The cost for these admissions totaled US $15 billion in aggregate.[1] Loop diuretics are the mainstay for managing fluid status in patients with heart failure. Unfortunately, in the presence of worsening congestion the absorption of oral loop diuretics is reduced, and their effectiveness is blunted.[2,3] For this reason, it is not surprising that 4 out of 5 CHF admissions occur specifically for the treatment of volume overload with intravenous (IV) therapy.[4] Moreover, nearly all of such hospitalizations are deemed uncomplicated since the sole intervention required is the IV agent to facilitate diuresis, and the dosage of the diuretic remains stable throughout the hospitalizations (without any need for escalation).[5] On average, such patients spend about 3 days in the hospital.

While optimizing oral diuretics remains the mainstay for treating worsening congestion, schemes also exist to allow for outpatient management of CHF exacerbations with IV diuretics; however, they are rarely utilized.[6] Among patients on Medicare, fewer than 1% of all CHF visits in the US are for outpatient IV diuresis, and among all visits specifically for the purpose of diuresis, outpatient IV diuresis accounts for no more than 15% of the total.[6,7]

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One of the challenges in reducing the burden and consequences of hospitalizations for a CHF exacerbation lies in being able to identify at presentation patients who medically are both not so acutely ill that outpatient management is obviously contraindicated, but who are at the same time at low risk for progression while hospitalized (ie, those for whom outpatient management would be adequate). Hence, we set out to define a group of short-stay CHF inpatients in the US hospitals whose sole reason for the admission is IV diuresis (CHF-L). We compared these patients to other more complicated and severely ill short-stay CHF patients (CHF-H) along their demographic and baseline clinical characteristics, hospital processes, and outcomes.

Methods

Data Availability

The data that support the findings of this study are derived from a proprietary database, Premier Healthcare database, which is available to researchers through a direct agreement with Premier.

Ethics Statement

Because this study used fully de-identified administrative data, it was exempt from ethics review under US 45 CFR 46.101(b)4.[8]

Study Design and Patient Population

We conducted a multi-center retrospective cohort study of adult patients (age >/= 18 years) hospitalized for management of CHF. Our case identification approach relied on a previously published administrative algorithm, as recommended by the ACC/AHA guidelines and included the following ICD-10-CM codes: I11.0, I13.0, I13.2, I50.1, I50.20, I50.21, I50.22, I50.23, I50.30, I50.31, I50.32, I50.33, I50.40, I50.41, I50.42, I50.43, I50.9.[9–12] To optimize the sensitivity of this algorithm we also included patients with DRG codes 291, 292, 293. Because we wanted to define a subpopulation of patients admitted specifically for the treatment of their CHF who could potentially avoid hospitalization, we included only those with the principal diagnosis of CHF and with the hospital length of stay (LOS) of four days or fewer. Patients were excluded if they had any of the following characteristics at admission (algorithms for all conditions available upon request):

1. Age <18 years
2. Hospital LOS > 4 days
3. Transferred from another acute care facility
4. Sepsis or severe sepsis or septic shock present on admission (POA)
5. Pneumonia POA
6. Acute respiratory failure/mechanical ventilation (MV) POA
7. Acute myocardial infarction (MI) POA
8. A major surgical procedure during hospitalization
9. Vasopressor administration on day 1
10. Hypertensive crisis POA
11. Patient status is NOT *nil-per-os* (nothing by mouth, NPO) during the first 2 days of hospitalization, as evidenced by receipt of at least one oral medication within the time frame

Data Source

The data source was the Premier Healthcare Database (PHD), an electronic laboratory, pharmacy and billing data repository, for years 2018 through 2021. PHD is a large geographically representative source of data for approximately 25% of all US admissions to acute care institutions. In addition to the standard information contained in typical hospital claims (those derived from the Uniform Billing-04 form, UB-04), such as patient age, sex, race/ethnicity, principal and secondary diagnoses and procedures, the database contains a date-stamped log of all items and services charged to the patient or their insurer, including all medications, laboratory tests, and diagnostic and therapeutic services. Premier assigns each patient a unique identifier, so

that previous and subsequent admissions to the same Premier hospital, along with principal and secondary diagnoses and procedure codes, can be readily ascertained. The database has been described in detail previously.[13–15]

Baseline Measures and Definitions

Potentially avoidable admissions (or CHF with low severity, CHF-L) were defined as those admissions without any markers of severe acute or chronic illness. Baseline characteristics included demographic data and type of insurance, as well as history of a hospitalization within the prior 30 days, comorbidity burden, and hospital characteristics. Charlson comorbidity score >2 was considered a signal of high chronic illness severity.[16] Additionally, the following events during the index hospitalization served as markers for high acute illness severity (CHF-H) (algorithms available upon request):

1. Cardiogenic shock
2. Acute respiratory failure
3. Acute MI
4. Acute renal failure
5. Dialysis
6. ICU admission
7. Cardiac catheterization[17]
8. Pulmonary artery catheterization
9. Arterial line placement
10. IACD or pacemaker procedure
11. The following physiologic alterations
    (a) Hypotension or vasopressor use
    (b) Hypoxemia
    (c) Oliguria
    (d) Altered mental status
    (e) Tachycardia
    (f) Bradycardia

Thus, hospitalizations of patients with Charlson score </= 2 and no factors defined determinative of severe acute illness were defined as potentially avoidable or CHF-L. All others were CHF-H and served as the comparator group. Other baseline characteristics included standard hospital and patients clinical and demographic characteristics. In addition to standard covariates, we explored the prevalence of prior hospitalization within 30 days of the index admission, as well as prior hospitalization within 30 days of the index admission for a surgical procedure.

Processes of Care During Index Hospitalization

To understand what further constraints, in addition to illness severity, could contribute to the need for hospitalization, we examined the prevalence and timing of the following procedures during the index hospitalization (Supplemental Table 1):

1. Intravenous diuretic use
2. O_2 administration
3. IV beta-blockers
4. IV ACE-I/ARB
5. IV calcium channel blockers
6. IV potassium
7. IV anticoagulation
8. IV afterload reduction use

Outcome Variables

The primary outcome of interest was hospital mortality. Secondary outcomes included hospital LOS, hospital costs, 30-day readmission rates among survivors, and discharge destination.

Statistical Analyses

Standard descriptive statistics were used to compare CHF-L to CHF-H group across demographics, comorbidities, hospital characteristics and processes, as well as hospital outcomes. Continuous variables are reported as means with standard deviations and as medians with 25th and 75th percentiles. Differences between mean values were tested via the Student's *t*-test, while those between medians were examined using the Mann–Whitney *U*-test. Categorical data are summarized as counts and percentages, and the Chi-square test or Fisher's exact test for cell counts <4 was used to examine between-group differences. While statistical significance was set at $p < 0.05$, because of the large size of the database, statistical significance does not necessarily translate to a clinically important difference. Because the purpose of the current study was to quantify the differences between those hospitalizations that may be avoidable and those that are not, we did not undertake statistical modeling to adjust for confounding when comparing the groups.

Results

Among 301,672 patients with a short-stay CHF admission, 135,304 (44.8%) met criteria for CHF-L. Compared to CHF-H, CHF-L subjects were less common in the Midwest and more common in the Northeast (Table 1). There were no important differences in their distributions based on hospital size, academic affiliation, or urbanicity. All markers of severity of acute illness were prevalent in the CHF-H only, as per cohort definition. Their distributions in that group can be found in the Supplemental Table 2. CHF-L patients were younger (mean age 70.5±14.1 vs 72.1±13.6 years, $p < 0.001$), more commonly female (48.6% vs 45.8%, $p < 0.001$), and less likely to be covered by Medicare (70.7% vs 78.6%, $p < 0.001$) than those with CHF-H. IV diuretics were more commonly given in the CHF-L group (91.8%) than in CHF-H group (82.2%) over the entire hospitalization and across different time periods examined ($p < 0.001$) (Figure 1). While CHF-L patients were more likely to receive IV ACE-I/ARB agents (0.5% vs 0.4%, $p = 0.003$), most other IV medications were more commonly utilized in the CHD-H group (Table 2). Notably, with the exception of anticoagulation, all other IV treatments examined were used in fewer than 5% of the patients in the first two days of hospitalization

Table 1 Baseline Characteristics

	CHF-L	%	CHF-H	%	P-value
	N = 135,204		N = 166,468		
Age, years					
Mean (SD)	70.5 (14.1)		72.1 (13.6)		<0.001
Median [IQR]	72 [60, 83]		74 [63, 83]		<0.001
Female, %	65,693	48.59%	76,301	45.84%	<0.001
Race					
White	97,665	72.24%	118,200	71.00%	<0.001
Black	24,768	18.32%	32,664	19.62%	
Asian	2152	1.59%	2901	1.74%	
Other	8267	6.11%	10,017	6.02%	
Unknown	2352	1.74%	2686	1.61%	

(*Continued*)

Table 1 (Continued).

	CHF-L	%	CHF-H	%	P-value
	N = 135,204		N = 166,468		
Hispanic	8992	6.65%	11,838	7.11%	<0.001
Admission Source					
Emergency Department	114,992	85.05%	143,131	85.98%	<0.001
Non-healthcare facility (including from home)	118,400	87.57%	146,056	87.74%	<0.001
Clinic	12,763	9.44%	14,381	8.64%	
Transfer from extended care facility	1628	1.20%	3113	1.87%	
Transfer from another non-acute care facility	1286	0.95%	1616	0.97%	
Other	1127	0.83%	1302	0.78%	
Admission type					
Surgical Medical	3479 131,725	2.57% 97.43%	4442 162,026	2.67% 97.33%	0.104
Observation	851	0.63%	1,016	0.61%	0.506
Hospital admission within prior 30 days (any)	37,249	27.55%	55,281	33.21%	<0.001
Acute myocardial infarction admission within prior 30 days	919	0.68%	1680	1.01%	<0.001
Surgical admission within prior 30 days	3837	2.84%	5527	3.32%	<0.001
Charlson Comorbidity Score*					
0	54,408	40.24%	22,054	13.25%	NA
1	43,160	31.92%	18,189	10.93%	
2	37,636	27.84%	44,257	26.59%	
3	0	0.00%	59,376	35.67%	
4	0	0.00%	14,808	8.90%	
5+	0	0.00%	7784	4.68%	
Mean (SD)	0.9 (0.8)		2.4 (1.5)		NA
Median [IQR]	1 [0,2]		2 [2,3]		NA
Insurance					
Medicare	95,563	70.68%	130,782	78.56%	<0.001
Medicaid	15,498	11.46%	14,705	8.83%	
Managed Care	11,432	8.46%	9925	5.96%	

(*Continued*)

Table 1 (Continued).

	CHF-L	%	CHF-H	%	P-value
	N = 135,204		N = 166,468		
Commercial	4292	3.17%	3911	2.35%	
Self-Pay	4896	3.62%	3350	2.01%	
Other	3523	2.61%	3795	2.28%	
Hospital Characteristics					
Census region					
Midwest	29,460	21.79%	39,988	24.02%	<0.001
Northeast	24,760	18.31%	27,760	16.68%	
South	62,266	46.05%	76,293	45.83%	
West	18,718	13.84%	22,427	13.47%	
Number of Beds					
<100	11,716	8.67%	13,752	8.26%	<0.001
100 to 199	23,174	17.14%	28,359	17.04%	
200 to 299	24,381	18.03%	30,009	18.03%	
300 to 399	23,694	17.52%	28,948	17.39%	
400 to 499	14,497	10.72%	18,132	10.89%	
500+	37,751	27.92%	47,268	28.39%	
Teaching	57,853	42.79%	71,446	42.92%	0.475
Urban	113,626	84.04%	140,651	84.49%	0.001

Note: *Heart failure excluded from the calculation.
Abbreviations: CHF-L, congestive heart failure low severity; CHF-H, congestive heart failure high severity; SD, standard deviation; IQR, interquartile range; NA, not applicable.

irrespective of the group. Anticoagulation, the most prevalent IV therapy in both groups, was administered to 23.8% of the patients in CHF-L vs 33.3% in CHF-H, $p < 0.001$.

Hospital mortality was lower in CHF-L (0.2%) than in CHF-H (1.5%) group. An additional 1.3% of CHF-L and 3.0% of CHF-H group were discharged to hospice ($p < 0.001$) (Figure 2). While a total of 85.7% in the CHF-L and 79.8% in the CHF-H groups were able to be sent directly home, more patients in the CHF-L group did not require home health care than in the CHF-H group (65.7% vs 56.5%, $p < 0.001$) (Figure 2). Despite similar durations of hospitalization (albeit statistically different), mean hospital costs in the CHF-L were substantially lower than those in CHF-H ($6,138 ± $5,558 vs $6,884 ± $6,124, $p < 0.002$). These trends in mortality, LOS, and costs persisted across all strata examined (Supplemental Table 3). Both all-cause (21.0% vs 26.2%, $p < 0.001$) and CHF-related (8.1% vs 10.5%, $p < 0.001$) 30-day readmissions were lower among persons classified as CHF-L than CHF-H.

Discussion

We demonstrate that nearly one-half of all short-stay hospitalizations for management of a CHF exacerbation are of low severity and, therefore, may be avoidable. By defining a group of patients whose only potential issue is diuresis, we have identified possible markers present at the time of acute presentation that may help clinicians in their decision-making process regarding which persons can be safely managed out of the hospital. Additionally, we have quantified the potential

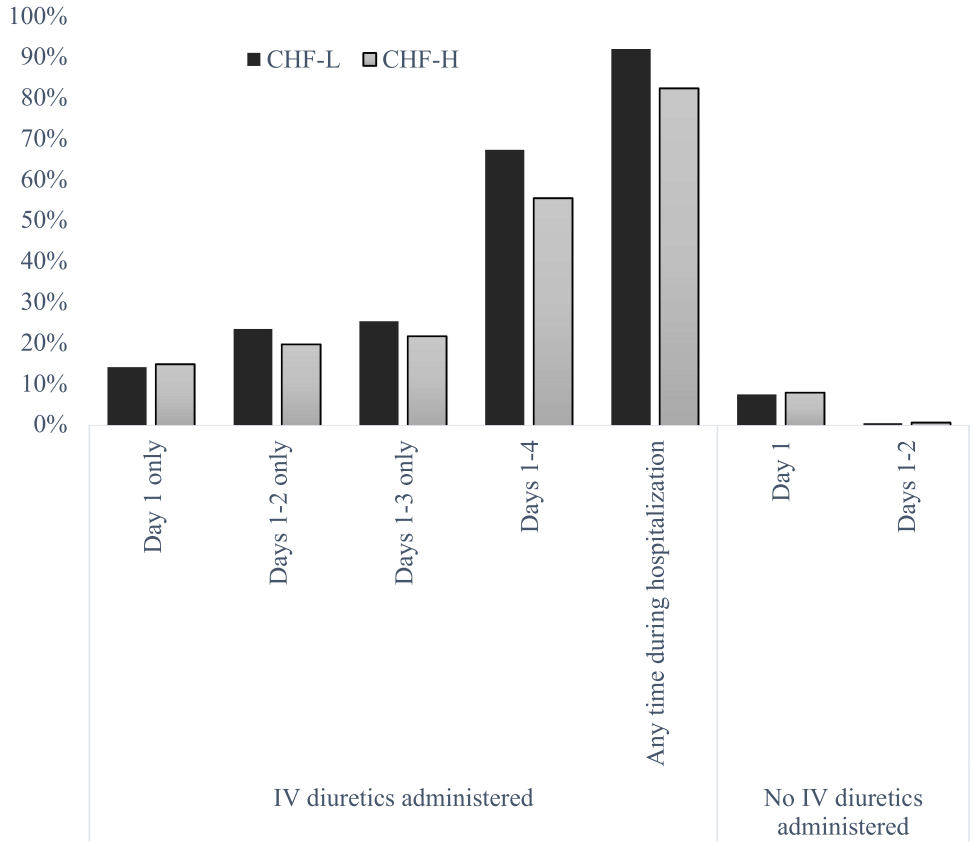

Figure 1 Intravenous diuretic administration*.
Note: *All comparisons reached statistical significance at $p < 0.001$.
Abbreviations: CHF-L, congestive heart failure low severity; CHF-H, congestive heart failure high severity; IV, intravenous.

economic consequences associated with avoiding hospitalization in this cohort. Assuming approximately 1 million annual admissions in the US for CHF exacerbations and a 4-day median LOS, of whom 45% are CHF-L, given the mean costs of around $6,000 per case (this number reflects the arithmetic mean of the costs for these patients' hospitalizations), avoiding these hospitalizations could result in annual savings of over $1.3 billion.[1]

Our study confirms several important points reported by others. First, only a small proportion of patients admitted for the management of worsening CHF require intravenous vasoactive agents. While the ADHERE registry noted that under ¼ of all of them receive these agents, our numbers are much lower.[18] This is likely in part due to the vastly differing time frames between the two studies (ADHERE reflects data from approximately 15 years ago, while ours is contemporary). Another probable reason for this disparity is the population differences, ours being only patients with a short-stay CHF admission. Hence, there was a reduced exposure time for these treatments in our study.

Prior work has borne out the idea that hospitalization costs constitute the vast majority of overall expenditures in the treatment of heart failure. That is, 80 cents out of every dollar spent on CHF are dedicated to inpatient treatment, of which 15% is specifically spent on the treatment of worsening heart failure.[19] It has been postulated that approximately 2/3 of all CHF admissions who require simply aggressive IV diuresis may be effectively treated as outpatients, resulting in billions of dollars in savings.[5] Despite this potential to avoid hospitalizations, emergency departments continue to admit the bulk of all patients presenting with a CHF exacerbation. The reasons for this are multifold.[20] First, as of 2015, the prevalence of outpatient IV diuresis infrastructure was less than 20%.[6] Second, and potentially more concerning, is that among those hospitals where IV diuresis infrastructure was available, these locations accounted for a disappointing 1.4% of all heart failure visits.[6] It is likely that the latter reflects a paucity of robust risk stratification strategies.

A review and recommendation statement by Collins et al addressed this lack of viable risk stratification strategies.[20] They proposed a two-tier ED-based evaluation to improve triaging of these patients such that more are able to avoid

Table 2 Intravenous Medications Other Than Diuretics Administered During Hospitalization

	CHF-L	%	CHF-H	%	P-value
	N = 135,204		N = 166,468		
Beta-blockers any time	5030	3.72%	6168	3.71%	0.827
Day 1 only	2933	2.17%	3138	1.89%	<0.001
Day 2 only	776	0.57%	1022	0.61%	0.156
Days 1 and 2 only	293	0.22%	376	0.23%	0.595
ACE-I/ARB	617	0.46%	641	0.39%	0.003
Day 1 only	467	0.35%	481	0.29%	0.006
Day 2 only	67	0.05%	61	0.04%	0.087
Days 1 and 2 only	20	0.01%	33	0.02%	0.300
Calcium channel blockers	647	0.48%	723	0.43%	0.072
Day 1 only	181	0.13%	249	0.15%	0.255
Day 2 only	173	0.13%	157	0.09%	0.005
Days 1 and 2 only	14	0.01%	73	0.04%	<0.001
Potassium	240	0.18%	402	0.24%	<0.001
Day 1 only	107	0.08%	158	0.09%	0.146
Day 2 only	45	0.03%	82	0.05%	0.033
Days 1 and 2 only	18	0.01%	40	0.02%	0.035
Anticoagulation	32,239	23.84%	55,378	33.27%	<0.001
Day 1 only	4537	3.36%	6373	3.83%	<0.001
Day 2 only	3306	2.45%	3835	2.30%	0.011
Days 1 and 2 only	4509	3.33%	7140	4.29%	<0.001
Afterload reduction/vasodilators	706	0.52%	1944	1.17%	<0.001
Day 1 only	78	0.06%	215	0.13%	<0.001
Day 2 only	37	0.03%	145	0.09%	<0.001
Days 1 and 2 only	115	0.09%	254	0.15%	<0.001

Abbreviations: CHF-L, congestive heart failure low severity; CHF-H, congestive heart failure high severity; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

hospitalization. Their schema is aimed at the middle portion of CHF exacerbations in the ED who neither respond fully to nor worsen following emergent treatment of their symptoms. While those who respond readily can be discharged without much risk, the group in the middle, those with a partial response, require further risk stratification. The authors suggest that certain high-risk features, such as ongoing symptoms, worsening renal function, elevated troponin levels, or the need for blood pressure support, would distinguish patients who do from those who do not require further inpatient management. The recommendation for those patients is for a period of observation instead of a full hospital admission.[20]

Despite availability of this stratification schema, more aggressive efforts at avoiding hospitalizations have not been successful. While it is estimated that nearly ½ of all patients presenting to the ED with worsening HF could be safely discharged home right away or after a short period of observation, in reality only under 5% end up in observation, and in

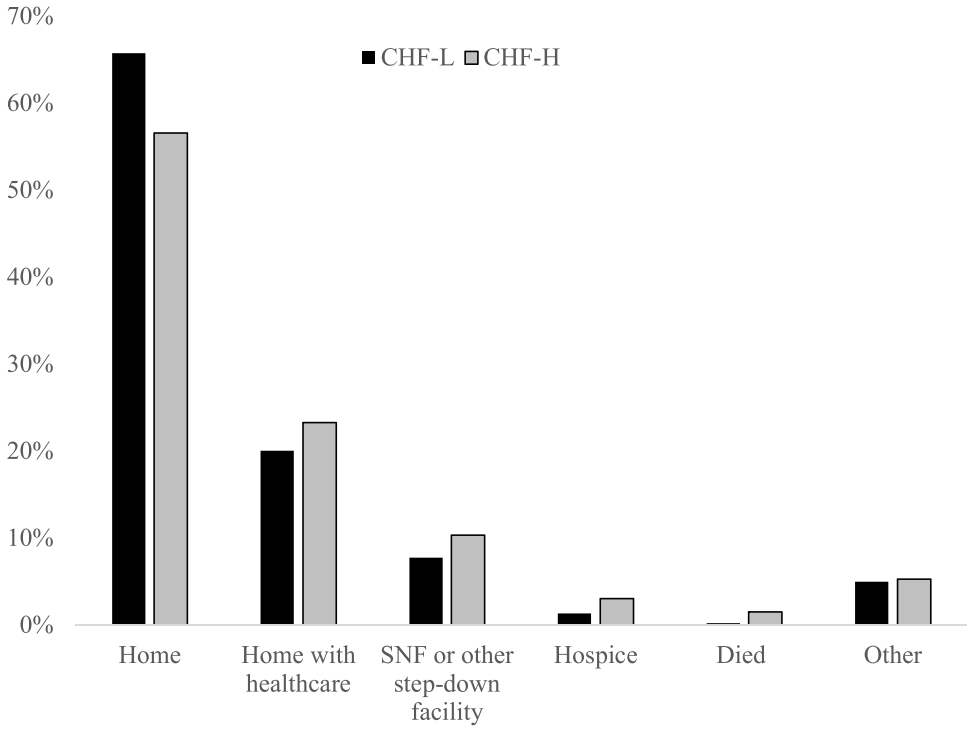

Figure 2 Discharge destinations*.
Note: *All comparisons reached statistical significance at $p < 0.001$.
Abbreviations: CHF-L, congestive heart failure low severity; CHF-H, congestive heart failure high severity; SNF, skilled nursing facility.

2015, nearly 30% of all CHF exacerbations presenting for treatment were treated as inpatients.[6] Our study narrows the population that may be a viable target for hospital avoidance strategies, as it focuses specifically on patients with not only brief stays (well under 1% of our cohort had the status of "observation") but also those not complicated by a heavy comorbidity burden or severe decompensation requiring aggressive hospital-based interventions. We build on prior efforts to paint a picture of what these patients may look like at the point of decision-making with respect to admission. That is, patients with low Charlson comorbidity scores and those who are not NPO, in shock, or requiring surgery or other procedures, constitute a significant fraction of all CHF admissions. If these patients were treated in the outpatient setting, they would not only avoid the inconvenience and risks associated with hospitalization but may save the already financially strained healthcare system over $1 billion annually.

Furthermore, finding viable alternatives for outpatient diuresis will also carry important implications for emergency departments. Following the global pandemic with SARS-CoV-2, hospitals continue to experience exceedingly high volumes, with emergency departments in particular being unusually busy with long wait times and staff shortages.[21] Robust alternatives to hospital-based evaluation and diuresis could mitigate at least some of this overload.

Our study has a number of strengths and limitations. Its major strength is the large number and a wide range of hospitals analyzed, lending our results generalizability. Our rigorous cohort definition reduces the risk and magnitude for a selection bias. Nevertheless, the retrospective nature of this study exposes our results to this potential. There is also a risk of misclassification, particularly as it relates to exposure. Because we used billing data to establish the prevalence of various interventions and severity markers, it is possible that a small number may have been undercoded. This may be true in particular for coding for physiologic markers, such as hypotension, hypoxemia, and related conditions. Underreporting of these conditions would result in classifying patients who may actually be CHF-H into the CHF-L category, thus overestimating the numbers of patients in this group. In the same vein, we did not have access to such clinical data as NYHA classification, natriuretic peptide measurements, or assessment of the left ventricular function, which makes our definitions prone to misclassification. To mitigate this, we utilized algorithms similar studies have used to answer similar questions. Confounding, while an issue in all

observational studies, is not a limitation, as we make no claims of causality or attribution, focusing instead simply on descriptive data.

Conclusions

In summary, we have shown that nearly one-half of all short-stay hospitalizations for a CHF exacerbation occur among low-risk patients and require almost exclusively IV diuresis. Although low-risk, ½ of them spend longer than two days in the hospital with the aggregate annual costs totaling $1.3 billion. Better outpatient alternatives could not only hold a considerable economic advantage but also help streamline patient care for both CHF and non-CHF patients presenting to the emergency department for evaluation.

Abbreviations

CHF, congestive heart failure; AHRQ, Agency for Healthcare Research and Quality; HCUP, Healthcare Cost and Utilization Project; NIS, Nationwide Inpatient Sample; IV, intravenous; CHF-L, low-severity CHF hospitalization; CHF-H, high-severity CHF hospitalization; LOS, length of stay; POA, present on admission; MV, mechanical ventilation; MI, myocardial infarction; NPO, *nil-per-os* (nothing by mouth); PHD, Premier Healthcare Database; UB-04, Uniform Billing-04 form; ACC, American College of Cardiology; AHA, American Heart Association.

Data Sharing Statement

The data that support the findings of this study are derived from a proprietary database, Premier Healthcare database, which is available to researchers through a direct agreement with Premier.

Ethics Statement

Because this study used fully de-identified administrative data, it was exempt from ethics review under US 45 CFR 46.101(b)4 [8].

Acknowledgments

No person other than the listed authors participated in the study, its design, or its reporting.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

MDZ's employer, EviMed Research Group, LLC, has received research grant support from scPharmaceuticals, Burlington, MA, USA. BHN's employer, OptiStatim, LLC, has received support from EviMed Research Group, LLC, Goshen, MA, USA. KS is an employee of scPharmaceuticals, Burlington, MA, USA. JFM is an employee scPharmaceuticals, Burlington, MA, USA. MG is an employee scPharmaceuticals, Burlington, MA, USA. AFS is a clinical consultant to and has received consulting fees from EviMed Research Group, LLC, Goshen, MA, USA. MDZ and AFS have received grant support and/or have served as consultants to Spero, Melinta, Pfizer, Astellas, Shionogi, and Lungpacer. The authors report no other conflicts of interest in this work.

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