ORIGINAL RESEARCH

In-hospital mortality rate and predictors of 30-day readmission in patients with iron deficiency anemia and diastolic heart failure: A cross-sectional study

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ABSTRACT

Introduction: There is currently strong evidence of the adverse effects of anemia on the prognosis of heart failure with reduced ejection fraction. Unfortunately, the data on the effects of anemia on a large sample of patients with diastolic heart failure (DHF) is lacking. In this study, we aimed to evaluate the effect of iron deficiency anemia on DHF readmission rates and its corresponding causes and burdens on the healthcare system.

Methods: We utilized 2018 Nationwide readmission data and included patients aged ≥18 years with ICD-10 CM code indicating acute or acute chronic diastolic heart failure and iron deficiency anemia was included in the study. The primary outcome is 30-day readmission rates. Secondary outcomes were mortality rates, common causes of readmission, and healthcare utilization. Independent predictors for readmission were identified using cox regression analysis.

Results: The total number of admissions in our study was 795,777. The mean age was 74.4 years (SD=13.7), and 63.54% were females. The 30-day readmission rate in patients with diastolic heart failure and iron deficiency anemia was 18.32 % vs. 16.01% in patients without anemia. The mortality rate at index admission and readmission was 3.62 % (2601) and 5.82 % (737), respectively. The most common cause of readmission was hypertensive heart and kidney disease with heart failure (17.74%). The independent predictors of readmission were age<85 years, household income < 59000$/per year, Medicare and Medicaid insurance, higher Elixhauser comorbidities score, longer Length of stay during the index admission, discharge to a nursing home,

hospital located in a large metropolitan area. The financial burden on healthcare for all the readmission was $837 million for 2018.

Conclusion: The 30-day readmission rate in patients with diastolic heart failure and iron deficiency anemia is 18.32% in the year 2018. The mortality rate increased from 3.62 % to 5.82 % with readmission. The financial burden for readmission during that year was $837 million. Future studies are warranted to treat iron deficiency anemia to prevent readmissions in diastolic heart failure.

INTRODUCTION

Heart failure is an extraordinarily pervasive problem affecting roughly 6.2 million people in the United States alone.[1] Correspondingly, the economic burden of the disease, comprising of related health care services, pharmacotherapies, and missed days of work, was estimated to be $30.7 billion in 2012.[2] In one European study, more than two-third of the 15 million heart failure patients were estimated to be re-hospitalized at least twice a year. [3] Therefore, re-hospitalization continues to remain a major concern for this disease. Common co-morbidities such as chronic obstructive pulmonary disease, hypertension, renal failure, and diabetes are often associated with heart failure and represent an important cause for readmission.[4]

An underestimated, but commonly occurring, co-morbidity in heart failure patients with preserved or reduced ejection fractions is anemia.[4, 5] Compared to the 10% of the general population afflicted with it, heart failure patients are much more likely to have anemia, with it presenting in 30% of stable ambulatory patients and 50% of acute decompensated heart failure patients.[6-9] Anemia in heart failure patients originates from complex interactions between impaired cardiac function, activation of neurohormonal and inflammatory response, drug effects, kidney dysfunction, and inadequate responses of the bone marrow.[10, 11] Several studies have indicated that it is associated with increased mortality and hospitalization.[6, 8, 9, 12]

There is currently strong evidence of the adverse effects of anemia on the prognosis of heart failure with reduced ejection fraction. Accordingly, clinical trials have been undertaken to study the effect of treatment in this cohort.[13, 14] Unfortunately, the data on the effects of anemia on a large sample of patients with diastolic heart failure (DHF) is lacking. Although previous studies have evaluated the in-hospital mortality and survival rates of patients with DHF with iron deficiency anemia, the sample sizes have been quite limited.[15, 16]

Therefore, this study aims to evaluate the IDA with DHF readmission rates and the corresponding causes and burdens it has on the on the healthcare system in a substantial sample size

METHODS

Data Source

A retrospective analysis was conducted using the largest publicly available all-payer database: Nationwide Readmissions Database (NRD) from year 2018.[17] NRD can be obtained from the Healthcare Cost and Utilization Project (HCUP), which is sponsored by the Agency for Healthcare Research and Quality (AHRQ). The unweighted 2018 NRD data contains approximately 18 million discharges for the year, while the weighted sample estimates around 35 million total discharges in the United States. NRD samples from 28 states, representing 59.7% of the total nationwide population and 58.7% of all United States hospitalizations.

Study Population
We included patients over the age of 18 years who were admitted to the hospital with a diagnosis of acute or acute on chronic diastolic heart failure and this group was further divided based on presence of a secondary diagnosis of Iron deficiency anemia. For reader's convenience any "DHF" mentioned in the manuscript refers to acute or acute on chronic diastolic heart failure and any "IDA" mentioned in the manuscript refers to iron deficiency anemia. Admissions from the month of December were excluded as data regarding 30-day readmissions were unable to be calculated as NRD does not track patients beyond one year. The International classification of disease (ICD) 10 Clinical modification (CM) was utilized to identify a patient sample, and ICD-10 procedure codes were used to obtain mechanical ventilation and vasopressor use.

Variable Selection
The variables included in the study were divided into three categories:
a) Patient Level: Age, sex, median household income in the zip code, insurance status, and Elixhauser comorbidity score.
b) Severity of Illness: Mechanical ventilation use, vasopressor use, length of stay (LOS), and disposition.
c) Hospital Level: Hospital location, teaching status, and bed size.

Study Outcomes
The primary outcome was all cause 30-day readmission. Readmissions were defined as any non-traumatic admission(s) within 30 days of initial discharge after index admission. Secondary outcomes were as follows:
a) In-hospital outcomes during index admission for DHF with anemia vs DHF without anemia
b) In-hospital outcomes during readmission for DHF with anemia
c) Top ten principal diagnoses in readmitted patients.
d) Total LOS and resource utilization associated with readmissions.
e) Independent predictors of readmission for DHF with anemia.

Statistical Analysis
All statistical analyses were conducted utilizing STATA version 17.0 (STATA CORP, College Station, Tx). Weights provided in the NRD dataset were applied for all analyses. P-values were all two sided, with <0.05 designated as statistically significant. For index admissions and readmissions, categorical variables were compared using the chi-square test. Continuous variables were compared using linear regression. Univariate cox regression was used to calculate the unadjusted hazard ratio. Multivariate cox regression model was used to identify the independent predictors.

RESULTS

Patient Characteristics
A total of 795,777 were included in the study of which 9.02% had DHF with IDA while 90.98 % had no IDA. Patient and hospital level characteristics of both groups are shown in Table 1. Women are 63.54% of all DHF with IDA, with a mean age of 74.4(SD 13.7). Seventy eight percent of the population was ≥65 years of age. 90.4% had either Medicare or Medicaid insurance. More than half were treated in large metropolitan area hospitals. In hospital mortality for index admission was 3.62% in DHF with IDA and 4.62% in DHF without IDA. Non-routine discharges (nursing home, home health or left against medical advice) are 60.14% in DHF with IDA and 57.5% DHF without IDA. Mean total length of stay

was 8.05 days in DHF with IDA patients and 6.88 days in DHF without IDA.

Table 1: Index hospitalization patient characteristics			
Variable	**DHF with IDA**	**DHF without IDA**	**p-Value**
Sample size (N=795,777)	**9.02%**	**90.98%**	
Age (years)			<0.001
18-44	3.06%	2.32%	
45-64	18.7%	19.13%	
65-84	53.12%	51.35%	
≥85	25.11%	27.2%	
Mean Age years (SD)			<0.001
Female	74.4(13.7)	75.8(13.08)	
Male	73.02(13.1)	72.5(13.62)	
Sex (Female)	63.54%	59.15%	<0.001
Median income in patients zip code ($)			0.10
<45,999	29.47%	28.7%	
46,000 – 58,999	28.39%	29.27%	
59,000 - 78,999	24.18%	24.18%	
>79,000	17.96%	17.86%	
Insurance			<0.001
Medicare	82.34%	83.35%	
Medicaid	7.56%	6.54%	
Private	8.63%	8.8%	
Uninsured	1.46%	1.31%	
Hospital location			<0.001
Large metropolitan area	56.22%	53.41%	
Small metropolitan area	35.07%	36.59%	
Micropolitan area	7.09%	7.97%	
Not metropolitan or micropolitan area	1.62%	2.03%	
Teaching hospital	70.33%	66.81%	<0.001
Hospital bed size			0.45
Small	19.31%	19.14%	
Medium	27.98%	28.71%	
Large	52.71%	52.15%	

Readmissions and Resource Utilization

The most common cause of readmission was hypertensive heart and kidney disease with heart failure (18.45%). Table 2 details the remaining ten most common reasons for readmissions. Thirty-day readmission rate was 18.32% in DHF with IDA and 16.01% in DHF without IDA. In-Hospital mortality was 3.62% (2601) during the index hospitalization, while 5.82% (737) died during readmission (3.62% vs 5.82%, p <0.001) in patients with DHF with IDA. Patients aged >65 years contribute to 87 % of deaths in both index admission and readmissions. The mean LOS for readmitted patients was 6.43 days, which is significantly lower when compared to the index admission LOS of 8.08 days (p <0.001). Mean hospitalization charges in readmitted vs index admission were $66,164 vs $79,608, respectively (p=0.01). Total LOS incurred due to readmission alone was 81,386 days with a resulting total hospitalization charge of $837 million.

Table 2: Most common all cause 30-day readmission

DHF with IDA		DHF without IDA	
1. Hypertensive hart and chronic kidney disease with heart failure and stage 1-4	17.74%	1. Hypertensive hart and chronic kidney disease with heart failure and stage 1-4	15.3%
2. Hypertensive heart disease with heart failure	7.39%	2. Hypertensive heart disease with heart failure	8.7%
3. Sepsis	6.08%	3. Sepsis	6.99%
4. Acute kidney Injury	4.85%	4. Acute kidney Injury	3.86%
5. Hypertensive heart and chronic kidney disease with heart failure and with stage 5 chronic kidney disease, or end stage renal disease	3.43%	5. Hypertensive heart and chronic kidney disease with heart failure and with stage 5 chronic kidney disease, or end stage renal disease	3.47%
6. Acute on chronic respiratory failure with hypoxia	2.17%	6. Acute on chronic respiratory failure with hypoxia	2.73%
7. Chronic obstructive pulmonary disease (acute) exacerbation	2.1%	7. Chronic obstructive pulmonary disease (acute) exacerbation	3.03%
8. Pneumonia	1.55%	8. Pneumonia	1.88%
9. Acute respiratory failure with hypoxia	1.52%	9. Acute respiratory failure with hypoxia	1.41%
10. Acute on chronic diastolic heart failure	1.5%	10. Acute on chronic diastolic heart failure	1.63%

Illness Severity
Compared to index admissions, readmissions had higher rates of mechanical ventilation (6.4% vs 5.66%, p <0.001), vasopressor use (1.4% vs 0.97%, p <0.001), and discharge to skilled nursing facility (32.17% vs 28.67%, p <0.001) or home health (28.73% vs 28.66% p <0.001). Comparison between index admissions and readmissions are shown in Table 3 and 4.

Independent Predictors of Readmission
As was aforementioned, variable selection and multivariate cox regression model building was utilized. The independent predictors for 30-day readmissions were a higher Elixhauser comorbidity score, age <85 years, Medicare and Medicaid insurance, non-routine discharge, income <$59,000, hospital location in large metropolitan area, and longer LOS. Predictors associated with decreased 30-day readmission were older age group (≥85 years), private insurance, routine discharge, hospital location in small metropolitan and micropolitan area, and mechanical ventilation. The other variables were not shown to be statistically significant enough to impact 30-day readmission rates, as is shown in Table 5.

Table 3: Index admission in-hospital outcomes

Variable	DHF with IDA	DHF without IDA	p-Value
Sample (N)	71,842	723,935	
30-day readmission rate	18.32%	16.01%	0.53
	[1]Adjusted HR for 30-day readmission 1.01(95% CI 0.97-1.03)		
Disposition			<0.001
Routine	39.76%	42.5%	
Nursing home transfer	29.69%	28.43%	
Home health	29.77%	28.15%	
Left against medical advice	0.79%	0.91%	
In-hospital mortality	3.62%	4.62%	<0.001
	[2]Adjusted OR for mortality 0.52(95%CI 0.49-0.55)		
Mean total hospitalization charge ($)	79,313 $	71,759 $	<0.001
Mean length of stay (days)	8.05	6.88	<0.001

[1]Adjusted Age, income level, elixhauser comorbidity score, insurance, hospital location, disposition and length of stay.
[2]Adjusted for Age, sex, income level, elixhauser comorbidity score, insurance, hospital location, bed-size and teaching status.

Table 4: Comparison between index admission and readmission in patients with DHF and IDA			
	Index	**Readmission**	**p-Value**
Sample	71,842	13,161 (18.32%)	
Died	2601 (3.62%)	737 (5.82%)	<0.001
18-44	1.36%	1.9%	
45-64	11.48%	13.09%	
65-84	51.8%	52.39%	
≥85	35.37%	32.61%	
Palliative/Hospice care			<0.001
18-44	1.56%	0.94%	
45-64	2.64%	4.04%	
65-84	5.36%	7.81%	
≥85	10.22%	16.93%	
Mechanical ventilation	5.82%	6.7%	0.01
Vasopressor use	0.97%	1.4%	0.001
Length of stay (days)	8.05	6.43	<0.001
Total charges ($)	79,608 $	66,164 $	<0.001
Disposition			<0.001
Regular	39.76%	33.55%	
SNF	29.69%	34.53%	
Home health	29.77%	30.83%	
AMA	0.79%	1.09%	

Table 5: Predictors of 30-day readmission in patients with DHF and IDA				
Factors	**Univariate HR (95% CI)**	**p-Value**	**[1]Multivariate HR (95% CI)**	**p-Value**
Age				
≥85	Reference		Reference	
65-84	0.87(0.74-1.02)	0.1	1.21(1.13-1.29)	<0.001
45-64	1.09(0.93-1.28)	0.24	1.33(1.2-1.48)	<0.001
18-44	1.14(0.97-1.34)	0.1	1.25(1.04-1.5)	<0.001
Female	0.99(0.94-1.04)	0.93	-	-
Median income ($)				
>79,000	Reference		Reference	
59,000 - 78,999	1.02(0.94-1.11)	0.56	1.02(0.93-1.11)	0.59
46,000 -58,999	1.09(1.013-1.019)	0.02	1.1(1.01-1.2)	0.02
<45,999	1.15(1.07-1.25)	<0.001	1.15(1.06-1.25)	<0.001
Insurance				
Private	Reference		Reference	
Medicare	1.15(1.05-1.26)	0.001	1.2(1.08-1.34)	<0.001
Medicaid	1.3(1.14-1.48)	<0.001	1.19(1.04-1.37)	0.008
Uninsured	1.08(0.86-1.36)	0.47	1.11(0.88-1.39)	0.34
Elixhauser comorbidity score	1.07(1.06-1.09)	<0.001	1.06(1.05-1.08)	<0.001
Hospital location				
Large metropolitan area	Reference		Reference	
Small metropolitan area	0.95(0.9-1.01)	0.13	0.94(0.88-1.01)	0.07
Micropolitan area	0.89(0.78-1.01)	0.07	0.86(0.76-0.98)	0.03
Not metropolitan or micropolitan area	1.002(0.79-1.26)	0.98	1.02(0.8-1.3)	0.84
Teaching hospital	0.98(0.92-1.04)	0.56	-	-
Hospital bed size				
Small	Reference		-	-
Medium	0.98(0.9-1.06)	0.66	-	-
Large	0.98(0.92-1.06)	0.74	-	-
Mechanical ventilation	0.96(0.84-1.09)	0.54	-	-
Vasopressor use	0.98(0.73-1.3)	0.89	-	-
Disposition				
Regular	Reference		Reference	
SNF	1.13(1.06-1.2)	<0.001	1.12(1.04-1.19)	<0.001
Home health	1.19(1.12-1.27)	<0.001	1.17(1.1-1.25)	<0.001
AMA	2.16(1.72-2.72)	<0.001	1.96(1.54-2.5)	<0.001
Length of stay	1.006(1.004-1.008)	<0.001	1.002(1.001-1.005)	0.04

[1]Adjusted Age, income level, elixhauser comorbidity score, insurance, hospital location, disposition and length of stay.

DISCUSSION

To the best of our knowledge, this is the first study investigating the clinical predictors and 30-day readmission rate of acute DHF or acute on chronic DHF patients with IDA in such a large sample population. IDA in diastolic heart failure of patients is associated with increased mortality in readmitted patients (3.62% vs 5.82% p <0.001), but did not increase 30-day readmission rate (18.32% vs 16.01%, p=0.53). While most common reason for readmission is almost identical in both the groups, IDA group had higher percentage of patients admitted with hypertensive heart and chronic kidney disease with heart failure (17.74% vs 15.3, p=0.01)

Prevalence of Anemia in Diastolic Heart Failure:

In this study, the prevalence of IDA was found to be approximately 9.02% in patients admitted for acute DHF. Of these, 63.54% were female. In a metanalysis of 1877 patients by Anna et al, found that prevalence of iron deficiency in DHF was 59%.[18] In a study of 303 patients, Latedo et al. found the prevalence of anemia in DHF patients was 58% compared to 43% in those with systolic dysfunction (p=0.01).[15] This study involves patients admitted with anemia and not just IDA. In another study of 294 patients with DHF, the prevalence of anemia was found to be 55% with 62% of DHF patients being female (p=0.017).[16] Silverbug et al. found more than half of all patients with congestive heart failure, both systolic and diastolic heart failure, have anemia. The degree of anemia was found to be directly related to the severity of heart failure.[19] In general, it can be said that there is a high prevalence of anemia in heart failure, likely more so in DHF than in SHF. A metanalysis study by Groenveld et al. found the prevalence of anemia in heart failure ranges from 7% to 60%, and its variability may be attributed to multiple factors including the definition of anemia used in that study.[20]

Clinical Implications:

In our study, the readmission rate in DHF patients with IDA was found to be 18.32% compared to 16.01% in those without IDA (p =0.53). Borut et al reported similar findings where rehospitalizations did not differ in iron deficiency and iron replete patients.[21] In Tehrani et al.'s study, no statistically significant difference in all-cause hospitalization (7.2 vs 7.5) or cardiac-related hospitalization (3 vs 3.6) at 5 years between the two groups was found.[16] In Latado et al.'s study, it was found that anemia was associated with higher in-hospital mortality in DHF patients at 24.3% compared to those who did not have anemia at 10.7%.[15] Tehrani et al. found the long-term mortality rates at 5 years to be statistically significant between the two groups at 57.4% in DHF with anemia compared to 43.2% in DHF without anemia.[16] They also found a shorter mean survival time in the anemic (37.8±1.8 months) group compared to non-anemic group (44.9±1.8 months) (p=0.01).[16] Martens et al reported that patients with iron deficiency had higher all-cause mortality.[22] CHARM program, the prevalence of anemia in patients with preserved and systolic EF was similar: 27% and 25%, respectively. [8]

In our analysis, in-hospital mortality during index admission was surprisingly lower in IDA with DHF patients than in non-IDA DHF patients (3.62% vs 4.62%, p <0.001) but readmitted patients with IDA during index admission had higher mortality (3.62% vs 5.82%, p <0.001), mechanical ventilation rate (5.82% vs 6.7%, p=0.01) and vasopressor use (0.97% vs 1.4%, p=0.001). Lower mortality during index admission might be due to possible interventions during index hospitalizations.

Further randomized studies are needed to validate this finding. There have been conflicting reports on whether the iron deficiency or anemia is the main contributor to the prognosis of heart failure patients. Jankowska et al.'s study of 546 patients found that iron deficiency, but not anemia, independently predicts all-cause mortality or heart transplantation.[23] Additionally, Okonko et al.'s study of 156 patients found iron deficiency as an independent predictor of increased mortality, regardless of hemoglobin levels[24] and similar results were published by Martens et al.[22] However, Parikh et al and Borut el at found no significant association between iron deficiency and all cause-mortality.[21, 25] While our study indicates that IDA in DHF increases the mortality if patients were readmitted in 30 days, further studies are required to understand the long-term effect of IDA in DHF.

Other Independent Predictors of Readmission:

In our study, we found that a higher co-morbidity score, older age (age >44 but <85 years), and longer LOS were all associated with a higher risk of readmission. This is consistent with the findings of studies done by Berkman et al.,[26] Gooding et al.,[27] and Chin et al.[28] on CHF patients. Patient's >85 years were at lower risk of 30-day readmission. This might be possibly due to higher palliative care consult/ hospice involvement and higher mortality during index admission. Krumholz et al. found an association of male sex, prior admission with CHF within the last 6 months, patients admitted on Medicare, multiple co-morbidities, and longer LOS to be associated with higher rates of readmission.[29] Although association of sex was insignificant in our study, we did find Medicare admission to be associated with a higher readmission rate. It is therefore reasonable to consider that these factors are associated with higher readmission risks and, in turn, a poorer prognosis in both systolic and diastolic heart failure.

Non-routine disposition was also associated with higher readmission risk in our study which, along with co-morbidity score and longer LOS, may indicate increased complexity and severity of disease and therefore contribute to the higher readmission rate. Additionally, the lowest income groups in our study had a significant association with poor prognosis and readmission. Tsuchihasi et al. had also found that unemployment and poor social support has a strong association in such cohorts.[30]

Limitations

As with any study, there were certain limitations. Namely, our study was retrospective in nature, which carries the inability to control patient exposure. Additionally, as this data was extracted from a database, other confounding variables may have affected the data, such as possible coding errors and failure of proper data entry. The database itself carried some limitations of not listing the patients' race or any pertinent lab values and/or imaging. Severity of IDA and possible interventions during admissions were unable to be obtained. December month admission had to be excluded as NRD does not track patients beyond calendar year. Out-of-state readmissions were also not recorded in the database. Lastly, we were unable to evaluate any social barriers during discharge or readmission, such as access to transportation, financial stability and resource accessibility, and general housing and living conditions.

CONCLUSION

To conclude IDA did not increase thirty-day readmission rate in patients with DHF

(18.32% vs 16.01%, p=0.53). However readmitted patients in IDA group had higher mortality, mechanical ventilation use and vasopressor use. Age < 85 years, low socioeconomic status, Medicare, Medicaid and higher co-morbidity score were independent predictors for thirty-day readmission. This study emphasizes the importance of long-term mortality and morbidity of IDA in DHF. Further randomized control trials are needed to understand the long-term effects of IDA in DHF.

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