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National Outcomes in Hospitalized Patients with Cancer and Comorbid Heart Failure

Running Title: Outcomes in Patients with Cancer and Heart Failure

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Abstract

Background: Heart failure (HF) and cancer are a significant cause of morbidity and mortality in the US. Due to overlapping risk factors, these two conditions often coexist.

Methods: We sought to describe the national burden of HF for hospitalized patients with cancer. We identified adults admitted with a primary oncologic diagnosis in 2014 included in the National Inpatient Sample (NIS). Patient hospitalizations were divided based on presence or absence of comorbid HF. Primary outcomes included cost, length of stay (LOS), and inpatient mortality. Logistic regression analysis with cluster adjustment was performed to determine predictors of inpatient mortality.

Results: There were 834,900 admissions for a primary oncologic diagnosis in patients without comorbid HF, and 64,740 (7.2%) admissions for patients with comorbid HF. Patients with HF were on average older and had more comorbidities. Patients with HF had significantly higher mean hospitalization cost ($22,571 vs $20,234, p-value <0.001), age-standardized LOS (12.7 vs 8.2 days, p-value <0.001), and age-standardized inpatient mortality (12.2% vs 4.5%, p-value <0.001). Presence of HF predicted inpatient mortality after adjusting for age, race, insurance payer, and comorbidity index (OR 1.12, 95% CI 1.04-20, p-value = 0.002).

Conclusions: Patients with cancer hospitalized with comorbid HF represent a high-risk population with increased costs and high inpatient mortality rates. More data is needed to determine what screening and treatment measures may improve outcomes.

Keywords: cancer, heart failure, hospitalization

Abbreviations:

HF = Heart failure

NIS = National Inpatient Sample

AHRQ = Agency for Healthcare Quality & Research

HCUP = Health Care Utilization Project

CCS = Clinical Classification Software

ICD-9-CM = International Classification of Diseases, version 9th revision, clinical modification

GI = Gastrointestinal

CPAP = Continuous positive airway pressure

LOS = Length of stay

CCR = Cost-to-Charge Ratio

Introduction

Heart disease and cancer are the most common causes of morbidity and mortality in the United States and together account for 1,229,772 (or 46.8%) of all deaths[1]. Heart failure (HF) alone afflicts 6.5 million people in the United States[2]. Heart disease and cancer share multiple risk factors such as age, tobacco use, diet, and lack of physical activity, and therefore the two conditions frequently coexist. Additionally, many effective and life prolonging chemotherapeutic agents may result in substantial cardiotoxicity leading to symptoms of cardiac dysfunction[3]. Over the last several years, the field of cardio-oncology has emerged with the aim of addressing the specific health needs of patients with cancer who are either at cardiovascular risk or have pre-existing heart disease. The population of cardio-oncologic patients is expected to increase in the near future due to our aging population. By the year 2030, the prevalence of HF is expected to increase by 46% resulting in >8 million adults with HF[2]. Similarly, by 2020, the number of cancer survivors is projected to increase from 11.7 million in 2007 to 18 million[4]. Although multiple studies have evaluated the effects of comorbidities on the prognosis of various cancer diagnoses, none to our knowledge have specifically described the relationship between HF and the outcomes of patients with cancer hospitalized in the U.S. Understanding this relationship may provide insights and opportunities for improving care of patients with cancer nationally. This study explores the risk of comorbid HF on hospitalized patients with cancer. We describe the national burden of HF as well as characterize the hospital events, procedures, and outcomes for hospitalized patients with cancer.

Methods

The National Inpatient Sample (NIS) from the Agency for Healthcare Quality & Research's (AHRQ) Health Care Utilization Project (HCUP) provides a representative sample of hospitalization administrative data in the U.S. For 2014, 20% of the 4,411 HCUP participating hospitals were sampled constituting an unweighted sample of over 7 million hospitalizations. The unit of analysis in the NIS is a discharge; therefore, readmissions are not identified. The NIS sampling frame covers over 95% of the United States population and 94% of all community hospital discharges[5].

All adult (age ≥18) patient hospitalizations with a primary cancer diagnosis were selected using the Clinical Classification Software (CCS) principal diagnostic codes (online supplementary material, Table 1). The CCS was developed by AHRQ as part of the HCUP to collapse International Classification of Diseases, version 9th revision, clinical modification (ICD-9-CM) codes into clinically meaningful and more useable categories[6]. There were 16 cancer diagnoses in total: head and neck, gastrointestinal (GI), lung, breast, female reproductive system, male reproductive system, renal, bladder, thyroid, Hodgkin lymphoma, non-Hodgkin lymphoma, leukemia, multiple myeloma, central nervous system (CNS), melanoma, and other unclassified malignancies. Patients with one of the following CCS codes were included in the "other cancer" category: 1) cancer, other and unspecified primary, 2) malignant neoplasm without specification of site or 3) neoplasms of unspecified nature or uncertain behavior. In an effort to exclude elective admissions for low-risk surgical procedures, admissions categorized as elective and lasting less than 48 hours in duration requiring surgical procedures were removed from the sample. Hospitalizations for primary oncologic conditions were categorized into

two groups, those without comorbid HF and those with HF to compare patient and hospitalization characteristics between cohorts (online supplementary material, Table 2). Select comorbidities and inpatient procedures were identified using relevant ICD-9-CM codes.

Outcomes of interest included hospitalization costs, length of stay (LOS), post-discharge disposition, and inpatient mortality. In order to characterize utilization of hospital services further, rates of multiple inpatient events were calculated including procedures and the diagnosis of circulatory shock. Procedures included were blood transfusions, inpatient chemotherapy, cardiac catheterization, dialysis, mechanical ventilation, continuous positive airway pressure (CPAP), thoracentesis, tracheostomy, and bronchoscopy.

Analyses of the patient characteristics and hospitalization costs accounted for the survey design of the NIS. Patient characteristics for the sample were described accounting for survey weights and clustering of data to make national estimates. Differences between groups were tested using t-tests and chi-squared tests as indicated by baseline characteristic. For the cost analysis, the NIS provides total charges, which reflect the amount a hospital billed for services, rather than actual costs or the amount a hospital received in reimbursement. To calculate costs, HCUP provides Cost-to-Charge Ratio (CCR) adjustments[7]. A known limitation of hospital-specific CCRs is that they do not account for all cost variations derived from hospital charges[8]. Cost to charge estimation is improved with further adjustment accounting for specific diagnosis-related groups[9]. The NIS CCR costs were further adjusted using the appropriate adjustment factor for each discharge's Medicare Severity Diagnosis Related Groups or CCS category to obtain the

final hospitalization cost estimates[8]. Differences between the groups were compared using t-tests or chi-square tests as indicated.

Multivariable logistic regression analysis was performed to identify factors associated with inpatient mortality. Models accounted for NIS survey design and clustering and adjusted for age, gender, race/ethnicity, median household income, comorbid HF, Elixhauser comorbidity score, and the cancer type using multivariable fractional polynomials for continuous risk factors. A graph of the curvilinear risk association between age and inpatient mortality, and Elixhauser composite score and inpatient mortality is included in the online supplementary material (Figures 1-2). The inpatient mortality odds ratios based on cancer type were calculated with respect to a reference category, which was defined as the cancer type associated with the lowest inpatient mortality rate. Analyses were performed in Stata 15.1 (StataCorp, College Station, TX). All estimation procedures were performed with appropriate NIS survey weights to account for sampling design, and results are presented as the weighted national 2014 hospitalized population using Stata's *svyset* estimation procedures. Institutional IRB provided exemption for this project[10].

Results

In total, there were 899,640 hospitalizations with a primary oncologic diagnosis in 2014. Of those, 834,900 (92.8%) patient hospitalizations did not have documented comorbid HF whereas 64,740 (7.2%) documented a comorbid HF diagnosis. Patient characteristics are shown in Table 1. Patients with HF were on average older (73.7 years versus 63.9 years old) than patients without HF. Patients with HF had more documented

comorbidities during the hospitalization overall, with particularly high rates of hypertension (74.1% versus 53.1%, p-value <0.001), coronary artery disease (46.0% versus 13.1%, p-value <0.001), and diabetes mellitus (40.3% versus 23.4%, p-value <0.001) compared to patients without HF. The most common oncologic diagnoses in patients with HF and without HF were GI (25.6% versus 26.1%, p-value = 0.2713), lung (17.7% versus 13.1%, p-value <0.001), and other (24.4% versus 25.3%, p-value = 0.0542) respectively.

Estimated hospitalization costs, LOS, inpatient mortality, and disposition data are reported in Table 2. The hospitalization cost and LOS for patients with HF was significantly higher than in patients without HF (mean adjusted cost $22,571 versus

Table 1

Characteristics of patients admitted with primary cancer diagnoses by heart failure status. CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CNS, central nervous system; DM, diabetes mellitus; GI, gastrointestinal; HTN, hypertension.

	No Heart Failure	**Heart Failure**	**P-value**
Total number of patients	834,900 (92.8%)	64,740 (7.2%)	<0.001
Age (SD)	63.9 (14.1)	73.7 (11.3)	<0.001
<65	49.3%	20.6%	
65-75	29.2%	31.4%	
>75	21.5%	48.0%	
Female	50.2%	46.3%	<0.001
Race			<0.001
White	67.7%	71.6%	
African American	12.1%	14.1%	
Hispanic	8.5%	5.3%	
Asian	3.2%	1.6%	

Primary Payer			<0.001
Medicare	49.4%	77.3%	
Medicaid	11.6%	5.6%	
Private	32.7%	13.5%	
Self-pay	2.9%	1.3%	
Cancer Types			
Head and neck	2.9%	1.8%	<0.001
GI (esophagus, stomach, colon, rectum and anus, liver, pancreas, other GI organs)	26.1%	25.6%	0.2713
Lung (bronchus lung, other respiratory)	13.1%	17.7%	<0.001
Breast	2.7%	1.9%	<0.001
Uterine (uterus, cervix, ovary, other female genital organs)	5.6%	3.8%	<0.001
Male genital (testicular, and other male genital)	2.3%	1.4%	<0.001
Renal (kidney, and other urinary)	4.1%	4.0%	0.6729
Bladder	2.7%	4.1%	<0.001
Thyroid	0.8%	0.4%	<0.001
Hodgkin Lymphoma	0.4%	0.2%	0.0009
Non-Hodgkin Lymphoma	3.8%	4.7%	<0.001
Leukemia	3.8%	5.5%	<0.001
Multiple Myeloma	1.9%	2.5%	<0.001
CNS	3.3%	1.1%	<0.001
Melanoma	0.2%	0.1%	0.1640
Other	25.3%	24.4%	0.0542
Comorbidities			
CAD	13.1%	46.0%	<0.001
Atrial Fibrillation	8.7%	36.0%	<0.001
HTN	53.1%	74.1%	<0.001
DM	23.4%	40.3%	<0.001
CKD	7.9%	27.3%	<0.001
COPD	14.6%	31.0%	<0.001
Liver disease	4.4%	4.7%	0.0398
Acute Stroke	1.6%	1.7%	0.4981

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Table 2

Age-standardized and unadjusted clinical and economic outcomes.

	No Heart Failure	Heart Failure	P-value
Unadjusted			
Median adjusted cost	$13,878	$14,450	
Mean adjusted cost	$20,234	$22,571	<0.001
Median length of stay (IQR)	5 (3-9)	7 (4-11)	
Mean length of stay	7.4	9.2	<0.001
Inpatient mortality	5.5%	10.1%	<0.001
Age-standardized			
Mean adjusted cost	$25,157	$39,053	<0.001
Mean length of stay	8.2	12.7	<0.001
Inpatient mortality	4.5%	12.2%	<0.001
Disposition			<0.001
Home/routine	54.7%	33.4%	
Home health care	22.0%	26.1%	
Skilled nursing facility	14.8%	27.5%	

$20,234, p-value <0.001; mean age-standardized LOS 12.7 days versus 8.2 days, p-value <0.001). The age-standardized inpatient mortality was 12.2% for patients with HF compared to 4.5% for patients without HF (p-value <0.001). Patients with HF were more often discharged to a skilled nursing facility compared to patients without HF (27.5% versus 14.8%).

Overall, the age-standardized rates of circulatory shock and most inpatient procedures were higher in patients with HF compared to those without HF (Table 3). Otherwise, differences in inpatient chemotherapy and tracheostomies were not markedly different.

Patient factors associated with inpatient mortality are shown in Table 4. Female gender was protective against inpatient mortality (OR 0.89, 95% CI 0.85 – 0.93, p-value

<0.001). Presence of HF was associated with a higher risk of inpatient mortality (OR 1.12, 95% CI 1.04-1.20, p <0.001). Adjusted ORs were most significant for the following cancers: lung (OR 4.67, 95% CI 2.96-7.37, p <0.001), breast (OR 3.74, 95% CI 2.35-5.97, p <0.001), non-Hodgkin lymphoma (OR 3.72, 95% CI 2.35-5.89, p <0.001), and leukemia (OR 7.53, 95% CI 4.79-11.86, p <0.001).

Discussion

This study describes the clinical characteristics, inpatient events, and outcomes of hospitalized patients with cancer and HF. Comorbid HF affects many patients with cancer (7.2%) who are admitted to the hospital with a primary oncologic diagnosis. Patients with cancer who have comorbid HF tend to be older, and commonly have a number of other comorbidities including coronary artery disease, atrial fibrillation, hypertension, diabetes mellitus, chronic kidney disease, and chronic obstructive

Table 3

Inpatient procedure rates by heart failure status for primary cancer-related hospitalizations. CPAP, continuous positive airway pressure. *p-values estimated from crude proportions. §age-standardization to 2000 U.S. Standard Population.

	No Heart Failure		**Heart Failure**		**P-values***
	Crude	Age-standardized§	Crude	Age-standardized§	
Shock	1.6%	1.5%	3.9%	10.7%	<0.001
Procedures					
Blood Transfusions	16.0%	17.2%	26.0%	31.6%	<0.001
Chemotherapy	6.7%	12.0%	6.3%	18.9%	0.1153
Cardiac Catheterization	0.2%	0.1%	1.5%	2.5%	<0.001
Dialysis	1.1%	0.9%	4.1%	8.1%	<0.001

Mechanical Ventilation	4.5%	4.2%	11.3%	15.7%	<0.001
CPAP	1.2%	1.0%	4.3%	4.4%	<0.001
Thoracentesis	6.8%	5.6%	12.8%	11.4%	<0.001
Tracheostomy	1.4%	1.3%	1.3%	2.0%	0.2205
Bronchoscopy	7.8%	5.5%	9.6%	9.1%	<0.001

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207**Table 4**

Patient factors associated with inpatient mortality during a primary cancer-related hospitalization. CNS, central nervous system; GI, gastrointestinal. *adjusted for age and Elixhauser comorbidity scores using multivariable fractional polynomials, as well as race, insurance payer, and median house income.	**OR**	**95% CI**	**P-value**
Female	0.89	0.85-0.93	<0.001
Heart Failure	1.12	1.04-1.20	0.002
Cancer Type			
Thyroid	*ref*.	*ref*.	*ref*.
Head and neck	1.71	1.05-2.78	0.032
GI (esophagus, stomach, colon, rectum and anus, liver, pancreas, other GI organs)	2.52	1.60-3.97	<0.001
Lung (bronchus lung, other respiratory)	4.67	2.96-7.37	<0.001
Breast	3.74	2.35-5.97	<0.001
Uterine (uterus, cervix, ovary, other female genital organs)	2.03	1.27-3.25	0.003
Male genital (testicular, and other male genital)	1.78	1.08-2.93	0.023
Renal (kidney, and other urinary)	1.13	0.69-1.83	0.631
Bladder	1.55	0.96-2.51	0.075
Hodgkin Lymphoma	2.87	1.60-5.15	<0.001
Non-Hodgkin Lymphoma	3.72	2.35-5.89	<0.001
Leukemia	7.53	4.79-11.86	<0.001
Multiple Myeloma	3.14	1.94-5.08	0.004
CNS	2.03	1.25-3.30	<0.001
Melanoma	5.66	3.16-10.12	<0.001
Other	3.43	2.18-5.39	<0.001

pulmonary disease. A comorbid HF diagnosis is associated with increased cost of hospitalization, LOS, and, most strikingly, a high inpatient mortality rate of 12.2%.

Comorbidities are important modifiers for the treatment and prognosis of cancer. Presence of multiple comorbidities has been associated with worse outcomes in multiple cancers including breast cancer[11], colon cancer[12], and lung cancer[13]. For example, Yancik et al[11] evaluated the effects of comorbidities in 1,800 postmenopausal breast cancer patients. They found that comorbid conditions such as diabetes, renal failure, stroke, liver disease, previous cancer, and smoking predicted early mortality. In the study's patient population, the second most common cause of death after cancer was heart disease (17.1% of all deaths). They concluded that both age and comorbidity status influence the ability to obtain adequate cancer prognostic information, limit treatment options and increase the chance of dying from a non-oncologic cause. In less aggressive cancers, comorbidity plays an even larger role in predicting survival[14].

To our knowledge, our study is the first to evaluate and characterize the national burden of HF among hospitalized oncologic patients. We found that the inpatient mortality rate of patients with cancer and HF (12.2%) is well above the average mortality rate of patients of a similar age admitted with acute decompensated HF (~4% mortality rate)[15]; however, it is similar to the rate of inpatient mortality for HF patients who required treatment in the intensive care unit (~11% mortality rate)[15]. HF may influence mortality rates for a number of reasons. First, as previously mentioned, HF alone is a significant cause of morbidity and mortality, and can carry a similar prognosis to many cancers[16,17]. In addition, HF often limits cancer treatment options as many

chemotherapeutic regimens exacerbate or even cause cardiac dysfunction and acute cardiovascular events. For example, anthracyclines, trastuzumab, cyclophosphamide, 5-fluorouracil, and certain tyrosine kinase inhibitors all have a significant incidence of HF[3]. Other chemotherapeutic agents, such as cisplatin, nilotinib and paclitaxel, are associated with acute coronary artery thrombosis[18]. Patients who receive suboptimal chemotherapy due to pre-existing HF or from developing cardiotoxicity during treatment can be at a high risk for poor outcomes.

Increasing efforts are being made to optimize the care of patients with cancer who have cardiovascular disease or have multiple cardiovascular risk factors both before and after cancer treatment. AHA recently published a scientific statement highlighting the preventive and treatment strategies for cardiovascular disease in breast cancer patients[19]. Recommendations for surveillance with echocardiography and strain imaging for cancer patients receiving cardiotoxic chemotherapy have recently been published by the American Society of Echocardiography and the American Society of Clinical Oncology, which reflects the growing efforts to identify patients at risk for poor cardiac outcomes[20,21]. While progress has been made in recognizing the specific care needs of patients with cancer and comorbid cardiac disease, cardiovascular management of a patient with cancer continues to be complex as it depends on the type of cancer, the cardiotoxicity profile of the chemotherapeutic regimen, as well as the patient's pre-existing cardiovascular risk factors. Here, we describe our findings that the hospitalized patient with cancer and heart failure suffers from poor outcomes, and thus highlight a potential opportunity for improvement in multidisciplinary care.

Future research is essential to better understand how to screen and manage hospitalized, high-risk patients with cancer. While our analysis of the NIS database is based on administrative data, a clinical registry of patients may offer opportunities to analyze the correlation of hospitalization outcomes with biomarker profiles and specific chemotherapeutic agents. Similarly, the Nationwide Readmissions Database enables analyses of national readmission rates and can be used for future studies evaluating the effect of heart failure on readmission rates for cancer patients. The utility of simple interventions such as early screening with cardiac biomarkers or imaging, or early involvement of the cardiology consulting team for hospitalized cancer patients with high cardiovascular risk also warrants evaluation.

Limitations

These data represent hospitalization episodes and not unique patients. The diagnostic codes used to identify HF are highly specific with reasonable sensitivity (~65%) and PPV of ~84%[22]. A clinical registry or cohort study may improve sensitivity to screen relevant patients for HF but would not provide the national scale of information provided through the NIS. This is a known shortcoming of administrative data from real-world patients. The NIS samples administrative data, thus more detailed data regarding symptoms, vital signs, chemotherapeutic agents, and laboratory data are not available. In addition, data on HF etiology, ejection fraction, functional status, and medical therapy are not available. There are significant limitations regarding the diagnosis of cancer, the stage of disease, and time in the clinical course (newly diagnosed and localized versus advanced disease after multiple treatments). Patients with certain cancer diagnoses may

be at a greater risk of mortality due to the intensity and modalities of therapy, and this information is not captured in the NIS database. The accuracy of diagnoses is dependent upon medical provider coding and certain diagnoses may be under-coded to a greater degree. Cost estimates are derived based on HCUP methodology and may not be accurate of true hospitalization costs. While we used Elixhauser comorbidity scores to adjust for comorbid factors associated with HF, other conditions prevalent among HF patients may impart risk to oncologic patients that was not accounted for in inpatient mortality regression model.

Conclusion

In conclusion, this study shows that cancer patients admitted to the hospital who have comorbid HF have higher costs, longer LOS, and high risk of short-term mortality. Prospective, longitudinal studies are needed to further assess the additional burden of HF in cancer patients. It is unclear whether earlier recognition and treatment of HF can affect outcomes, however this warrants further investigation with a collaborative effort between oncologists and cardiologists.

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