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ORIGINAL RESEARCH ARTICLE

Health care utilization and mortality associated with heart failure-related admissions among cancer patients

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Abstract

Aims Heart failure (HF) outcomes continue to improve with widespread use of new therapies. Concurrently, cancer survival has dramatically improved. Yet whether cancer patients share similar strategies and outcomes of inpatient HF treatment to those without HF is unknown. We sought to assess the contemporary impacts of cancer on inpatient HF outcomes over time.

Methods and results The retrospective National Inpatient Sample (2003–15) and National Readmissions Database (2013–14) registries were queried for adults admitted for HF and stratified for cancer status, excluding cases of metastatic disease. Temporal trends in HF admissions, hospital charge rates, length of hospitalization, HF-related procedure utilization, in-hospital mortality, and hospital readmissions were analysed. Over 13 years of follow-up, there were 12 769 077 HF admissions (mean age 73 years, 50.8% female, 30.8% non-White), among which 1 413 287 (11%) had a co-morbid cancer diagnosis. Cancer patients were older, were predominantly male, and tended to be smokers. Over time, HF admission rates among cancer patients increased, despite a concurrent decrease among patients without cancer ($P < 0.0001$). After propensity matching, in-hospital mortality was significantly higher among cancer HF patients (5.1% vs. 2.9%, $P < 0.0001$). Additionally, HF-related procedure utilization was disproportionately lower among cancer patients (0.30 vs. 0.35 procedures/HF hospitalization, $P < 0.001$); the presence of cancer was associated with increased costs, length of hospitalizations, and all-cause readmissions, but fewer HF readmissions ($P < 0.0001$, each).

Conclusions While the incidence of HF hospitalizations has increased among cancer patients, they do not appear to share the same rates of advanced HF care, readmissions trends, or reductions in in-hospital mortality. Future studies targeting modifiable factors related to these differences are needed.

Keywords Cancer; Heart failure; National Inpatient Sample; National Readmissions Database

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Introduction

Cardiovascular disease (CVD) and cancer represent two of the largest contributors to mortality in the USA.[1,2] There is substantial evidence to suggest that cancer and CVD have shared modifiable, as well as non-modifiable, risk factors.[2] Interestingly, among cancer survivors with pre-existing CVD, the risk of death from cardiovascular causes exceeds that due to cancer recurrence.[3] This may be due in part to cardiac toxicities associated with ongoing or prior cancer therapies.[4,5] Yet the treatment of modifiable CVD risk factors in the presence of underlying cancer has been linked with improved long-term cancer prognosis.[6]

The rise of new cancer therapies has led to significant improvement in cancer-related mortality over the last two decades.[7] Unfortunately, with improved survival, the trade-off has seen a dramatic increase in the incidence of non-cancer-related events, including CVD and incident heart failure (HF).[4] Specifically, the impact of these conditions has appeared to limit outcomes and survival during or following cancer therapies. HF due to cancer therapy has been associated with a 3.5-fold increase in mortality, when compared with that in patients who develop idiopathic cardiomyopathy.[8] However, the exact nature and modifiable factors associated with these outcomes are not well understood. Furthermore, there are emerging data to suggest that HF patients with a concurrent cancer diagnosis, irrespective of prognosis, may not receive the same contemporary HF strategies seen among non-cancer populations.[8]

While there is increasing focus on investigating the relationship of cancer to HF development, there remains much uncertainty around differences in treatment, readmission, and in-hospital mortality rates. Moreover, an improved understanding of hospital and patient-level factors unique to this rapidly growing population of patients with HF and concomitant cancer may enhance the ability to provide more effective therapies. As such, we sought to assess the modern impacts of cancer on inpatient HF management, cost, and in-hospital mortality over time.

Methods

Data source

The National Inpatient Sample (NIS) is an inpatient database in the USA[9] developed by the Agency for Healthcare Research and Quality (AHRQ). In the present study, we used data from 1 January 2003 through 30 September 2015. National Readmissions Database (NRD) is a nationally representative AHRQ hospitalization and re-hospitalization dataset.[10] For this study, we utilized 2013 and 2014 NRD datasets (*Figure* S1). The structure of each dataset is explained in details in the Supporting Information.

Study population and variables

We used *International Statistical Classification of Diseases*, Ninth Revision, Clinical Modification (*ICD-9-CM*) codes to identify all hospitalized adults (≥18 years) who had a primary diagnosis (*DX1* of NIS) of HF (425, 428, 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, or 404.93). The discharge diagnoses and procedures were recoded using the clinical classification of diseases software (CCS) into broad categories, available as separate variables within the NIS and NRD dataset. We used the CCS coded discharge diagnoses to further define our initial cohort, where we identified HF exclusively using the code 108 (*DXCCS1* only). In this constructed cohort, we then identified cancer patients using *DXCCS* codes (*DXCCS1–DXCCS30*) 11-45. NIS and NRD provide 29 co-morbidities (also known as Elixhauser's co-morbidity measures) on the basis of *ICD-9-CM* diagnoses, and the diagnosis-related group in effect on the date of discharge. These co-morbidities are not directly related to the principal diagnosis or the main reason for admission and are likely to have originated before the hospital stay.[11] Hospitalizations with the co-morbidities of cancer were included in the cancer cohort. All patients who did not have either the *DXCCS* codes listed earlier, or the listed specific co-morbidities, were considered non-cancer patients. Patients with an identified co-morbidity of metastasis were excluded from the cancer cohort.

The NIS variables included in the study were demographic characteristics (age, sex, and race), income quartile, insurance status, hospital-level characteristics, co-morbidities, and procedures. For utilization analyses, procedures were identified using various *ICD-9-CM* procedure codes or *PRCCS* codes provided by NIS (all codes listed in the Supporting Information). The procedures of interest were echocardiography, cardiac catheterization, percutaneous coronary intervention, mechanical ventilation, inotrope use, mechanical circulatory support, and implantable cardioverter defibrillator implantation (*Table* S1). In 2015, the Healthcare Cost and Utilization Project (HCUP) State Inpatient Database was used to create two indices based on 29 co-morbidity measures designed to predict in-hospital mortality (morscore) and 30 day readmission.[12] Those indices were calculated for our cohort as well.

During cohort creation in NRD, HF admissions were tagged for all adults who presented in the years 2013 through 2014, during the first 11 months of each year, because NRD does not maintain year-to-year linkage. The patients were followed up for 30 days post-discharge to identify any readmissions. In another parallel analysis, 9 months of each year was used to assess 90 day readmission rates. Data elements utilized in NRD were the primary DXCCS discharge diagnosis. A list of all discharge diagnoses were created using DXCCS1 via the CCS codes as reflected in recent NRD-based investigations.[13] All patients who died during the index admission, or had missing length of stay information, were excluded from the aforementioned analysis.

Outcomes

The NIS provided data on specific outcomes of interest, including hospitalization charges, length of stay, in-hospital mortality, and discharge disposition, by cancer status. Actual cost of hospitalization was obtained by multiplying each hospital's charges with their cost-to-charge ratios[14] and wage

index for a given year. The wage index helps correct for geographic variations in costs among hospitals.[14] Charges and costs were inflation adjusted to 2015.[15] We also assessed differences in procedure utilization. In addition, NRD was utilized to analyse reasons for 30 day readmission, in both the cancer and non-cancer cohorts.

Statistical analysis

Annual variance analysis for NIS datasets was performed using the DOMAIN method for all years.[16] DOMAIN was also used for the 2013–14 NRD dataset to ensure accurate estimates and variance.[17] We followed the recommendations from AHRQ for analysis using survey data.[17] Survey-specific statements with hospital and patient-level weights were used to obtain national estimates. The Rao–White χ^2 test was used to compare categorical variables, and a survey-specific *t*-test was used for continuous variables. We used the Cochran–Armitage test of trend for categorical variables and survey-specific linear regression for continuous variables. Hospital charges and length of stay were log-transformed because they were not normally distributed, and geometric mean was presented.[18,19] For a length of stay of 0 days, a value of 0.0001 was imputed to avoid negative log values. All figures and tables, excluding *Figure 4*, were obtained from NIS analysis.

Three separate triennial cohorts from 2003–05, 2008–10, and 2013–15 were created. Insurance status, hospital level, co-morbidities, procedure use, and NIS provided outcomes are presented. We utilized all cancer and non-cancer admissions for each year as denominators for comparative annual trends. Subgroup analyses by gender and age $<$ 50 years are all presented in the tables.

Modelling for in-hospital mortality and procedural utilization was performed using methodology underscored subsequently. Unadjusted trends and morscore stratified trends are presented. As morscore is confounded, with higher scores in cancer patients, year-to-year comparison for in-hospital mortality and total procedure utilization were performed using a propensity-score-matched design. The propensity score is a number that represents the relationship between multiple characteristics and the dependent variable as a single characteristic[20] (Methods S1).

The HCUP-defined methodology[3] was utilized to define 30 day readmissions after an index event of HF. The number of readmissions and causes for readmission were compared across cancer and non-cancer patients using the Rao–White χ^2 test.

Subgroups of breast cancer, lung cancer, colon cancer, prostate cancer, and lymphoma were created, and the crude HF admission rates and in-hospital mortality rates were determined. The same rigour as described earlier, including variance analysis, was performed to ensure the integrity of the estimates.

All analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, North Carolina), and the description of methodology is presented in graphical form in *Figure* S1.

Results

A total of 12 769 077 HF admissions were identified between 2003 and 2015 from NIS, using the primary discharge diagnosis of HF. Within these HF admissions, an estimated 1 413 287 (11%) had a co-morbid non-metastatic cancer diagnosis. Moreover, the prevalence of different cancer subtypes was as follows: 20.0% breast cancer, 8.3% lung cancer, 11.6% colon cancer, 17.6% prostate cancer, and 15.1% leukaemia and lymphoma.

Characteristics of patients

Patient demographics and hospital characteristics among HF hospitalizations were analysed over three triennial cohorts (2003–05, 2008–10, and 2013–15) to better understand hospital and patient-level factors over time (*Table 1*). Patients admitted with HF and cancer were older, more commonly men, and more likely to have pre-existing HF and valvular heart disease. However, the HF patients with concomitant cancer had lower rates of traditional CVD risk factors, including hypertension, diabetes, obesity, and tobacco use. Over the study period, mean age stayed the same in both groups, while traditional CV risk factors such as diabetes, hypertension, obesity, and smoking status significantly increased in both the groups. A list of non-traditional risk factors is shown in *Table 1*. Mean Elixhauser's readmission score and Elixhauser's mortality score were significantly higher in the cancer cohort compared with the non-cancer cohort (2013–15 cohort readmission score of 38.9 ± 0.1 vs. 21.2 ± 0.0 and mortality score of 16.2 ± 0.1 vs. 5.8 ± 0.0, respectively; $P < 0.0001$ for both).

Heart failure admissions over time

Over time, HF admission rates among cancer patients increased, despite a concurrent decline among non-cancer patients ($P < 0.0001$ for both trends; *Figure 1A*). This trend was most evident in female patients with cancer compared with male patients (*Figure 1B*, *Figure S2A*). Moreover, this increasing trend in HF admissions among cancer patients was also noted in subgroup analyses of younger-aged patients (age $<$ 50 years) (*Figure S2B*).

We then sought to explore HF admission trends when stratified by specific cancer types. Prostate cancer had the

Table 1 Patient-level and procedural characteristics of hospitalizations with heart failure

	2003–05			2008–10			2013–15[a]		
	Cancer (n = 106 320)	Non-cancer (n = 3 194 804)	P-value	Cancer (n = 110 564)	Non-cancer (n = 2 780 013)	P-value	Cancer (n = 102 230)	Non-cancer (n = 2 371 039)	P-value
Patient characteristics									
Age, years (mean ± SE)	75.4 ± 0.1	72 ± 0.1	<0.0001	75.6 ± 0.1	71.8 ± 0.2	<0.0001	75.2 ± 0.1	71 ± 0.1	<0.0001
18–39 years (%)	0.6	2.5	<0.0001	0.6	2.7	<0.0001	0.5	2.8	<0.0001
40–59 years (%)	8.8	17.4		8.8	18.7		9	19.8	
60–79 years (%)	49.9	44.4		48.3	41.5		49.9	42.7	
≥80 years (%)	40.6	35.7		42.3	37.1		40.6	34.7	
≥65 years (%)	84.1	72	<0.0001	83.5	70.1	<0.0001	83.2	68.2	<0.0001
Women, %	44.4	53.1	<0.0001	43.6	50.4	<0.0001	44	48.6	<0.0001
Race, %			<0.0001			<0.0001			<0.0001
White	75.7	69		74.9	66.1		73.5	65.1	
Black	14.6	18.4		15.4	20.8		16.8	21.9	
Hispanic	6.4	8.8		5.6	7.9		5.5	8.1	
Asian or Pacific Islander	1.6	1.6		1.4	1.9		1.9	2.1	
Native American	0.2	0.3		0.5	0.7		0.3	0.5	
Other	1.6	1.9		2.2	2.6		2	2.3	
Income quartiles[b]			<0.0001			<0.0001			<0.0001
0–25	28.3	33.4		27.4	33.3		27.9	34.6	
26–50	26.2	27		26.3	27.3		26.2	26.8	
51–75	24.4	22.2		23.7	21.8		23.8	22	
76–100	21.1	17.3		22.6	17.5		22.2	16.6	
Co-morbidities (%)									
Traditional cardiovascular									
Cardiomyopathy	1.1	0.8	<0.0001	1.3	1.2	<0.0001	2.2	1.1	<0.0001
Peripheral vascular disease	6.3	8.4	<0.0001	9.6	10.8	<0.0001	12.7	12.7	0.58
Valvular heart disease	1.1	0.6	<0.0001	0.8	0.5	<0.0001	0.8	0.4	<0.0001
Hypertension	47	53.5	<0.0001	59.7	64.8	0.001	67.7	70.9	<0.0001
Diabetes	30	39.7	<0.0001	34.2	43.1	<0.0001	39.2	47.2	<0.0001
Obesity	3.7	8.6	<0.0001	7.5	14.4	<0.0001	13	22	<0.0001
Non-traditional									
Weight loss	3.2	1.7	<0.0001	5.9	3.1	<0.0001	9	4.5	<0.0001
AIDS	0.1	0.2	0.026	0.3	0.2	0.62	0.2	0.2	0.86
Anaemia	27.8	19.9	<0.0001	36.6	27.5	<0.0001	40.3	31.4	<0.0001
Arthritis and collagen vascular disease	1.5	2	<0.0001	2.3	2.5	0.14	2.9	3	0.31
Chronic liver disease	1.5	1.7	0.014	2.3	2.4	0.87	3.6	3.6	0.24
Chronic renal disease	14.8	15.6	0.035	33.5	37.1	<0.0001	43	44.6	<0.0001
Chronic lung disease	36.5	33.8	<0.0001	36.6	35.1	0.0001	37.9	38.2	0.16
Hypothyroidism	9.6	10.9	<0.0001	14.2	14.4	0.03	17.9	17.1	0.44
Neurologic	5.2	6	<0.0001	6.7	8	<0.0001	7.2	8.6	<0.0001
Psychiatric	6.5	7.6	<0.0001	10.3	70.8	0.01	12	13.8	<0.0001

(*Continues*)

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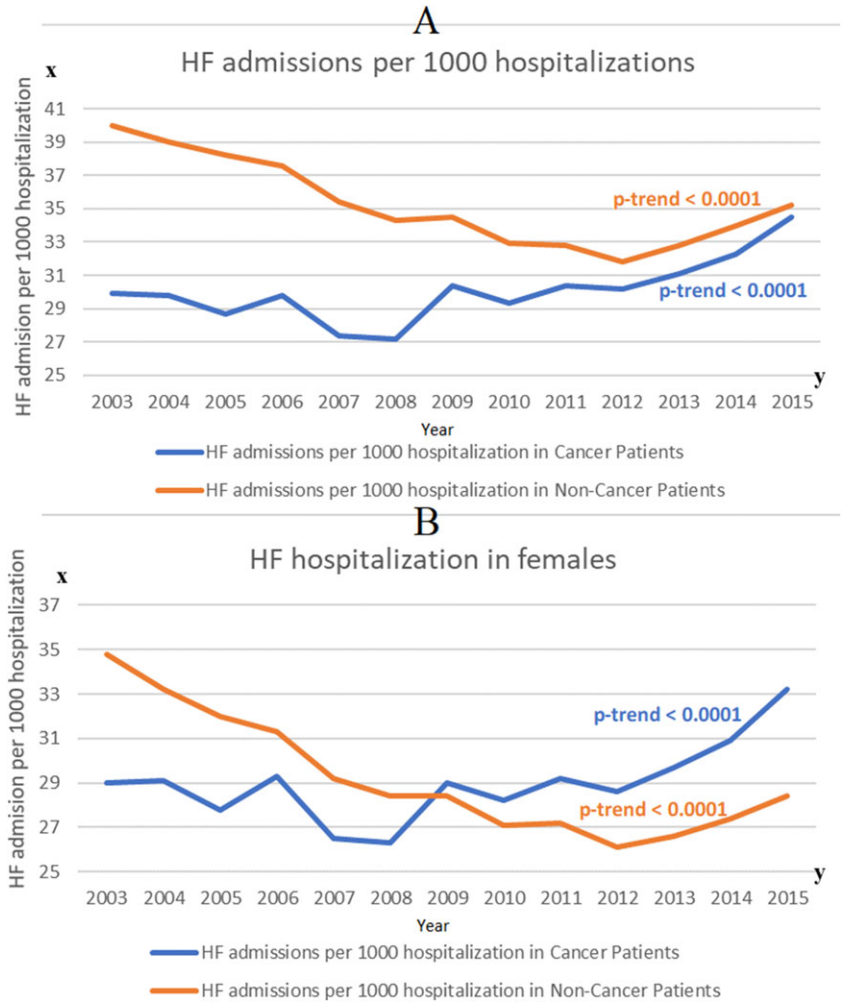
Table 1 (continued)

	2003–05			2008–10			2013–15[a]		
	Cancer (n = 106 320)	Non-cancer (n = 3 194 804)	P-value	Cancer (n = 110 564)	Non-cancer (n = 2 780 013)	P-value	Cancer (n = 102 230)	Non-cancer (n = 2 371 039)	P-value
Fluid/electrolyte disorder	23.2	20.3	<0.0001	27.9	25.8	<0.0001	35.8	33	<0.0001
Coagulation disorder	5.1	2.6	<0.0001	7.2	3.9	<0.0001	10.4	5.9	<0.0001
Substance abuse	1.4	3.5	<0.0001	2.1	4.7	<0.0001	3.1	6.4	<0.0001
Smoker	10.9	11.8	0.001	19.5	19.3	0.7	33.2	32	0.02
Total Elixhauser's co-morbidities									
0	0	9.5	<0.0001	0	4.3	<0.0001	0	2.3	<0.0001
1	8	19.4		4.7	13.0		2.3	8.3	
2	23.2	27		14.7	21.3		8.5	16.5	
≥3	68.8	44.1		80.7	61.4		89.2	72.9	
Elixhauser's readmission score (mean ± SE)	29.9 ± 0.1	12.8 ± 0.1	<0.0001	35.2 ± 0.2	17.9 ± 0.1	<0.0001	38.9 ± 0.1	21.2 ± 0	<0.0001
Elixhauser's mortality score (mean ± SE)	13 ± 0.1	3.3 ± 0	<0.0001	14.7 ± 0.1	4.8 ± 0.04	<0.0001	16.2 ± 0.1	5.8 ± 0	<0.0001
Procedures (%)									
Echocardiography	5.4	5.6	0.21	6.3	6.3	0.8	6.8	7.1	0.19
Coronary angiography	5	8.3	<0.0001	5.6	8.5	<0.0001	6.5	9.6	<0.0001
Percutaneous coronary intervention	0.6	0.9	<0.0001	0.7	1	0.0002	0.8	1	0.002
Mechanical ventilation	5.2	4.9	0.004	5.8	5.7	0.3	9.5	9.3	0.3
Inotrope use	0.1	0.1	0.87	0.4	0.4	0.5	0.6	0.5	0.48
Mechanical circulatory support	0.4	0.8	<0.0001	0.5	0.9	<0.0001	0.4	1.1	<0.0001
ICD implantation	0.5	1.4	<0.0001	0.7	1.9	<0.0001	0.5	1	<0.0001

[a]Only data till September 2015 presented.
[b]Median household income quartiles based on patient zip code.

Figure 1 Trends in heart failure hospitalization. (A) Trends in heart failure hospitalization over 13 years. Presented per 1000 hospitalizations. Over time, HF admission rates among cancer patients increased, despite a concurrent decline among non-cancer patients ($P < 0.0001$ for both trends). (B) Trends in heart failure hospitalization in female patients. Over time, HF admission rates among cancer patients increased, with trend being most evident in female patients with cancer.



highest incidence of HF admissions, whereas lung cancer had the lowest. Furthermore, HF admission rates among cancer patients increased significantly over time in all cancer types (*Figure S2C*). Additionally, HF admission rates among cancer patients with metastatic disease have been also shown in context to cancer patients without metastatic disease as well as non-cancer patients (*Figure S2D,E*).

In-hospital mortality

Overall unadjusted in-hospital mortality rates followed a decreasing trend among all groups over time (*P*-trend < 0.0001 for cancer vs. 0.0003 for non-cancer group). However, the risk of in-hospital mortality was significantly higher among those with cancer over time (5.1% vs. 2.9%, $P < 0.0001$; *Figure 2A*). This trend was even more evident in cancer hospitalizations with HCUP mortality scores > 15 (*Figure 2B*).

Although HF admissions in lung cancer were lower than those in other cancer types, in-hospital mortality rate was the highest. Similarly, although HF admissions in lymphoma were higher than in other cancer types, in-hospital mortality rate was the lowest. Additionally, in-hospital mortality rates among cancer patients decreased significantly over time in all cancer types (*Figure S3*).

Figure 2C shows the in-hospital mortality for propensity-score-matched analyses from four different time periods (2004, 2008, 2012, and 2015). Over the study period, in-hospital mortality continued to decrease in both the groups ($P < 0.0001$). However, in-hospital mortality was consistently higher in the cancer group when compared with the non-cancer group ($P < 0.0001$ for all years). Furthermore, after

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risk adjustment, mortality rates in the cancer group did not attenuate over time [2004, 2008, 2012, and 2015 OR and 95% confidence interval of 1.9 (1.7–2.2), 1.8 (1.6–2.0), 1.6 (1.4–1.9), and 1.7 (1.4–2.0), respectively] *Figure 2C*.

Analysing disposition at discharge demonstrated that 43% of patients with cancer were discharged home and that 49% required a skilled nursing facility or home health care. Comparatively, 51% of non-cancer patients were discharged home, and 42% of non-cancer patients required a skilled nursing facility or home health care ($P < 0.0001$ over time; *Table 2*).

Cancer status and procedure use during heart failure admission

During the study period, lower in-hospital HF-related procedure utilization rates were noted among cancer patients compared with non-cancer patients (0.30 vs. 0.35 procedures/HF hospitalization, $P < 0.001$; *Table 1*). Specifically, there were significantly fewer cancer patients undergoing coronary angiography with or without coronary intervention, mechanical circulatory support, and cardiac defibrillator implantation over time ($P < 0.01$ for all; *Table 1*, *Figure S4A–G*). Moreover, this was more evident when stratified by AHRQ mortality score, even in the presence of a low mortality score ($P < 0.0001$; *Figure 3A,B*).

Over the study period, the frequency of cardiac procedures increased, irrespective of cancer status. However, cardiac procedure utilization was consistently lower among cancer patients when compared with non-cancer ($P < 0.01$ for all years). *Figure 3C* shows all cardiac procedures for propensity-score-matched analyses by time period (2004, 2008, 2012, and 2015). Further, even after risk adjustment, the utilization of cardiac procedures in the cancer group did not increase over time [adjusted odds ratio (OR) 0.9 (0.8–

Figure 2 In-hospital mortality rates in heart failure with cancer. (A) Unadjusted in-hospital Mortality rates. Overall unadjusted in-hospital mortality rates followed a decreasing trend among all groups over time (*P*-trend < 0.0001 for cancer vs. 0.0003 for non-cancer group). However, the risk of in-hospital mortality was significantly higher among those with cancer over time (5.1% vs. 2.9%, $P < 0.0001$). (B) In-Hospital mortality divided into the three risk groups on the basis of Healthcare Cost and Utilization Project (HCUP) mortality score. Non-cancer mortality trend presented for reference. In-hospital mortality trend was even more evident in cancer hospitalizations with HCUP mortality scores > 15. (C) Propensity-matched mortality in patients with cancer vs. non-cancer over four different years (*C*-statistic for matching using age, sex, race, insurance status, number of Elixhauser's co-morbidity, hospital bed size, hospital location and teaching status, and geographic region of the hospital; 2004, 2008, 2012, and 2015—0.7, 0.7, 0.7, and 0.6, respectively). Over the study period, in-hospital mortality continued to decrease in both the groups ($P < 0.0001$). However, in-hospital mortality was consistently higher in the cancer group when compared with the non-cancer group ($P < 0.0001$ for all years). Furthermore, after risk adjustment, mortality rates in the cancer group did not attenuate over time [2004, 2008, 2012, and 2015 odds ratio (OR) and 95% confidence interval (CI) of 1.9 (1.7–2.2), 1.8 (1.6–2.0), 1.6 (1.4–1.9), and 1.7 (1.4–2.0), respectively].

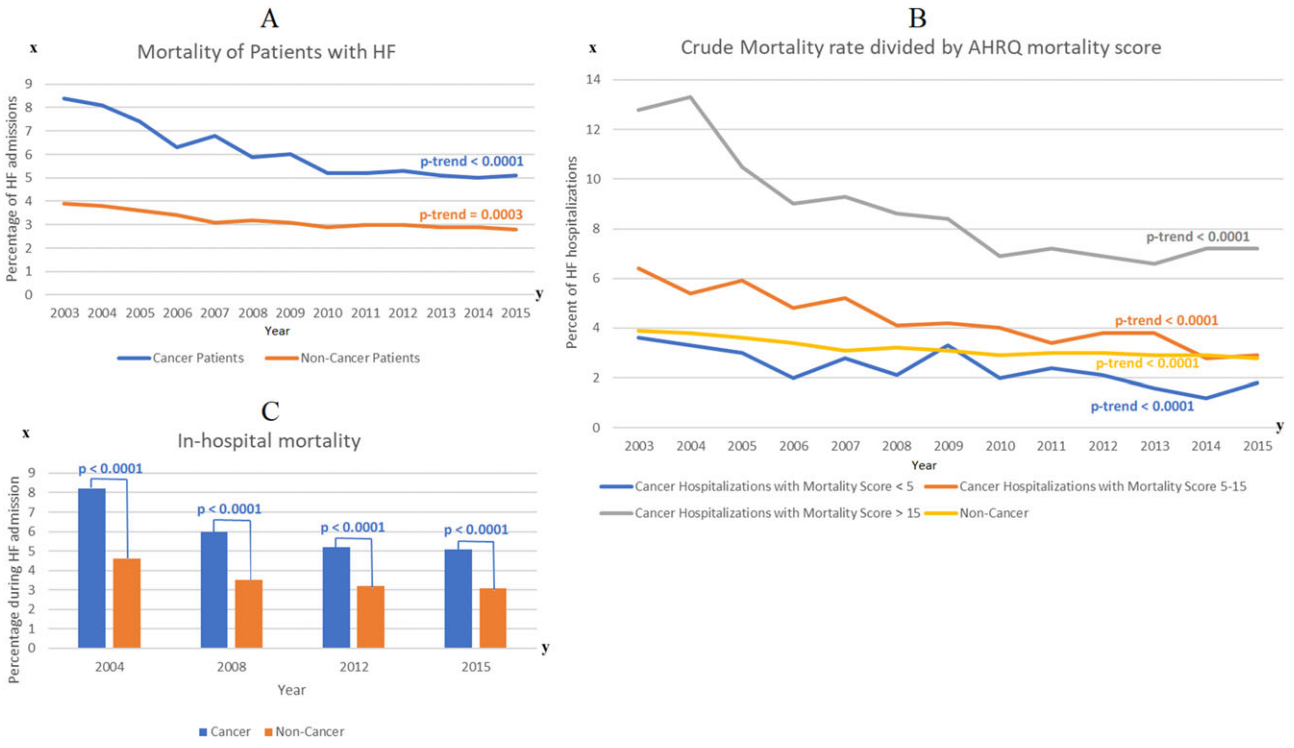

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Table 2 Outcomes of hospitalizations with heart failure

	2003–05			2008–10			2013–15[a]		
	Cancer (n = 106 320)	Non-cancer (n = 3 194 804)	P-value	Cancer (n = 110 564)	Non-cancer (n = 2 780 013)	P-value	Cancer (n = 102 230)	Non-cancer (n = 2 371 039)	P-value
Outcomes									
Length of stay (mean ± SE, days)	4.2 ± 0.1	3.6 ± 0.03	<0.0001	3.9 ± 0.1	3.5 ± 0.03	<0.0001	4 ± 0.0.03	3.6 ± 0.01	<0.0001
Total hospital charges (mean ± SE, US$)[b]	21 320 ± 390	20 031 ± 313	0.007	25 625 ± 480.5	24 383 ± 422	0.6	30 400 ± 280	28 160 ± 184	0.01
Total hospital costs (mean ± SE, US$)[c]	8489 ± 126	7792 ± 93.9	<0.0001	8612 ± 116	7994 ± 97	0.02	8694 ± 71	7857 ± 43	<0.0001
Unadjusted mortality, %	8	3.8	<0.0001	5.7	3.1	<0.0001	5.1	2.9	<0.0001
Disposition			<0.0001			<0.0001			<0.0001
Home	49.7	58.9		47	54.7		42.5	51.1	
Short-term hospital	3	3.7		2.5	3.1		2.4	3	
Skilled care facility	19.5	17.5		20.5	19.1		21.1	19.5	
Home health care	19.3	15.2		23.7	18.8		28.3	22.2	
Against medical advice	0.4	1		0.5	1.1		0.6	1.3	
Unknown	0.1	0.04		0.1	0.1		0.1	0.1	

[a]Only data till September 2015 presented.
[b]Adjusted to inflation.
[c]Using HCUP cost-to-charge, wage index adjustment along with inflation adjustment.

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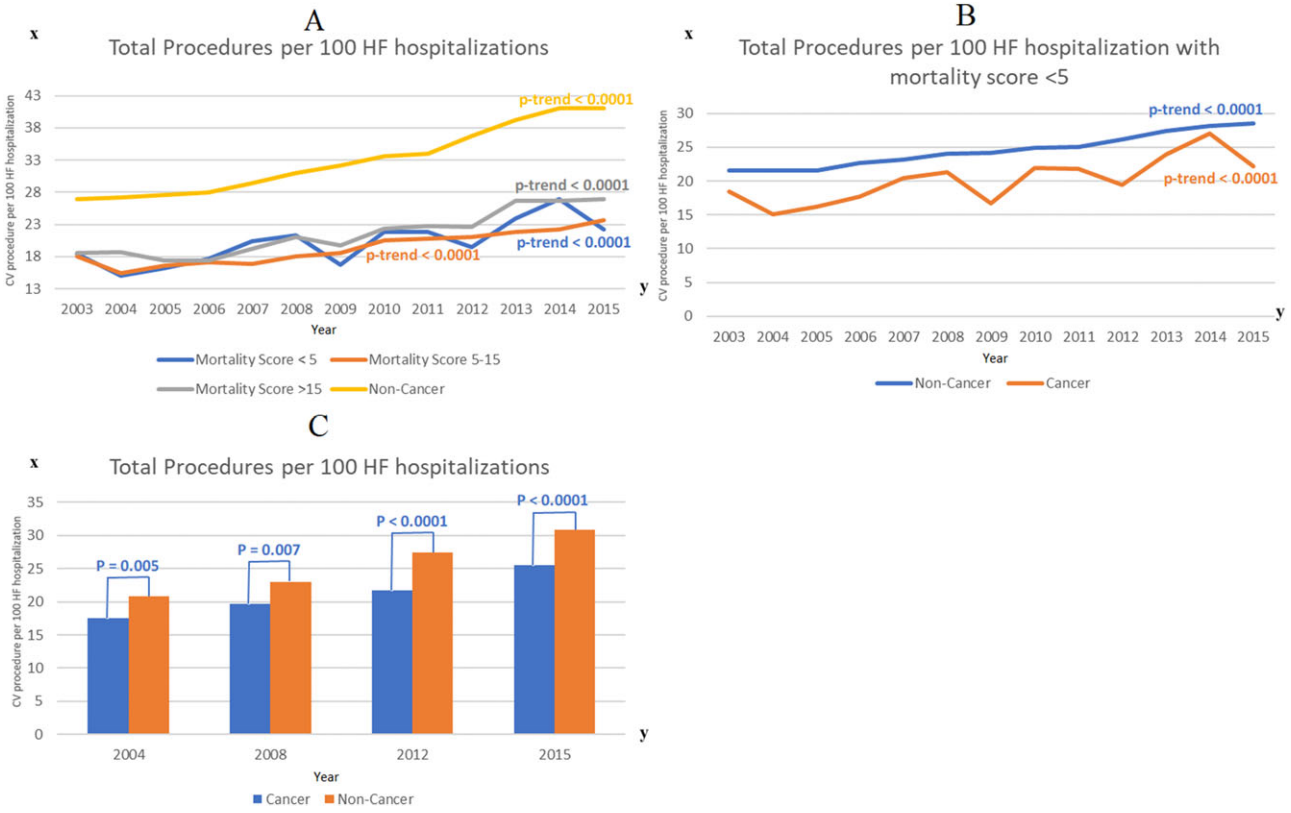
Figure 3 Cardiac procedures in heart failure with cancer. (A) Aggregate of all aforementioned cardiac procedures stratified by Agency for Healthcare Research and Quality (AHRQ) mortality score. Year-to-year comparison between groups in cancer cohort not significant but is significant in the non-cancer cohort. During the study period, lower in-hospital HF-related procedure utilization rates were noted among cancer patients compared with non-cancer patients (0.30 vs. 0.35 procedures/HF hospitalization, $P < 0.001$). (B) Aggregate of all aforementioned cardiac procedures with AHRQ mortality score < 5. Cardiac procedure utilization was especially less evident in cancer hospitalizations with AHRQ mortality scores < 5. (C) Propensity-matched total procedures utilized in patients with cancer vs. non-cancer over four different years (*C*-statistic for matching using age, sex, race, insurance status, number of Elixhauser's co-morbidity, hospital bed size, hospital location, and teaching status and geographic region of the hospital; 2004, 2008, 2012, and 2015—0.7, 0.7, 0.7, and 0.6, respectively). Over the study period, the frequency of cardiac procedures increased, irrespective of cancer status. However, cardiac procedure utilization was consistently lower among cancer patients when compared with non-cancer patients ($P < 0.01$ for all years). Further, even after risk adjustment, the utilization of cardiac procedures in the cancer group did not increase over time [adjusted OR 0.9 (0.8–0.9), 0.9 (0.8–0.95), 0.8 (0.7–0.9), and 0.8 (0.8–0.9) for 2004, 2008, 2012, and 2015, respectively].



0.9), 0.9 (0.8–0.95), 0.8 (0.7–0.9), and 0.8 (0.8–0.9), for 2004, 2008, 2012, and 2015, respectively]. Additional trends for utilization of specific cardiac procedures in the cancer as well as non-cancer groups are shown in *Figure S4A–G*.

Length of stay, cost of care, payment source, and discharge disposition

In unadjusted analyses, HF admissions among cancer patients had increased lengths of stay (4.0 vs. 3.6 days, $P < 0.0001$) and increased hospitalization costs ($8694 vs. $7857, $P < 0.0001$) than had HF admissions among HF patients without cancer diagnoses at the index visit (*Table 2*). These relationships were consistent over all triennial cohorts. Nearly 86% of HF hospitalizations in cancer patients, compared with 83% in the non-cancer group, were billed to Medicare/Medicaid ($P < 0.0001$; *Table 3*). These trends were consistent over the study period. Additional hospital-level and insurance characteristics are shown in *Table 3*.

Readmissions

Patients with cancer saw higher 30 day overall readmission rates following index HF admission (22.5% vs. 20.2%, $P < 0.0001$). However, specific HF-related readmission rates were lower in those with cancer when compared with those without (29% vs. 35%, $P < 0.0001$) (*Figure 4*). Moreover, haematologic and infection-related readmission rates were higher among cancer patients (23% vs. 12%, $P < 0.0001$ together).

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Table 3 Hospital-level and insurance characteristics of hospitalizations with heart failure

	2003–05			2008–10			2013–15[a]		
	Cancer (n = 106 320)	Non-cancer (n = 3 194 804)	P-value	Cancer (n = 110 564)	Non-cancer (n = 2 780 013)	P-value	Cancer (n = 102 230)	Non-cancer (n = 2 371 039)	P-value
Teaching hospital (%)	35.8	35.5	0.81	40.6	40.4	0.7	57.1	54.8	<0.0001
Bed size, (%)			0.08			0.2			<0.0001
Small	11.9	12.9		13.1	13.8		16.9	18.3	
Medium	25.8	25.5		24.1	23.8		28.2	28.8	
Large	62.3	61.6		62.8	62.4		54.9	52.9	
Region (%)			<0.0001			<0.0001			<0.0001
Northeast	20.2	19.7		23	20.5		22.2	19.5	
Midwest	27	23.7		25.2	23.2		24.7	22.6	
South	37.6	42.1		36.4	41.1		36.8	41.8	
West	15.2	14.4		15.4	15.2		16.3	16.1	
Hospital in urban location, (%)	82.4	82.2	0.96	84.2	83.7	0.5	88.3	87.1	<0.0001
Weekend admission (%)	22.4	21.8	0.047	22.5	22.3	0.5	23	23	0.9
Elective admission (%)	9.9	10.8	0.006	8.5	9	0.07	6.3	6.6	0.2
Payment source (%)			<0.0001			<0.0001			<0.0001
Medicare	82	74.8		79.8	71.9		81.6	72.2	
Medicaid	3.7	7.7		4.4	8.6		4.7	10.1	
Private	12.1	12.7		13.2	13.7		11.3	12.1	
Self-pay	1	3		1.1	3.6		0.9	3.4	
No charge	0.1	0.3		0.1	0.4		0.1	0.4	
Others	1.1	1.5		1.4	1.8		1.5	1.9	

[a]Only data till September 2015 presented.

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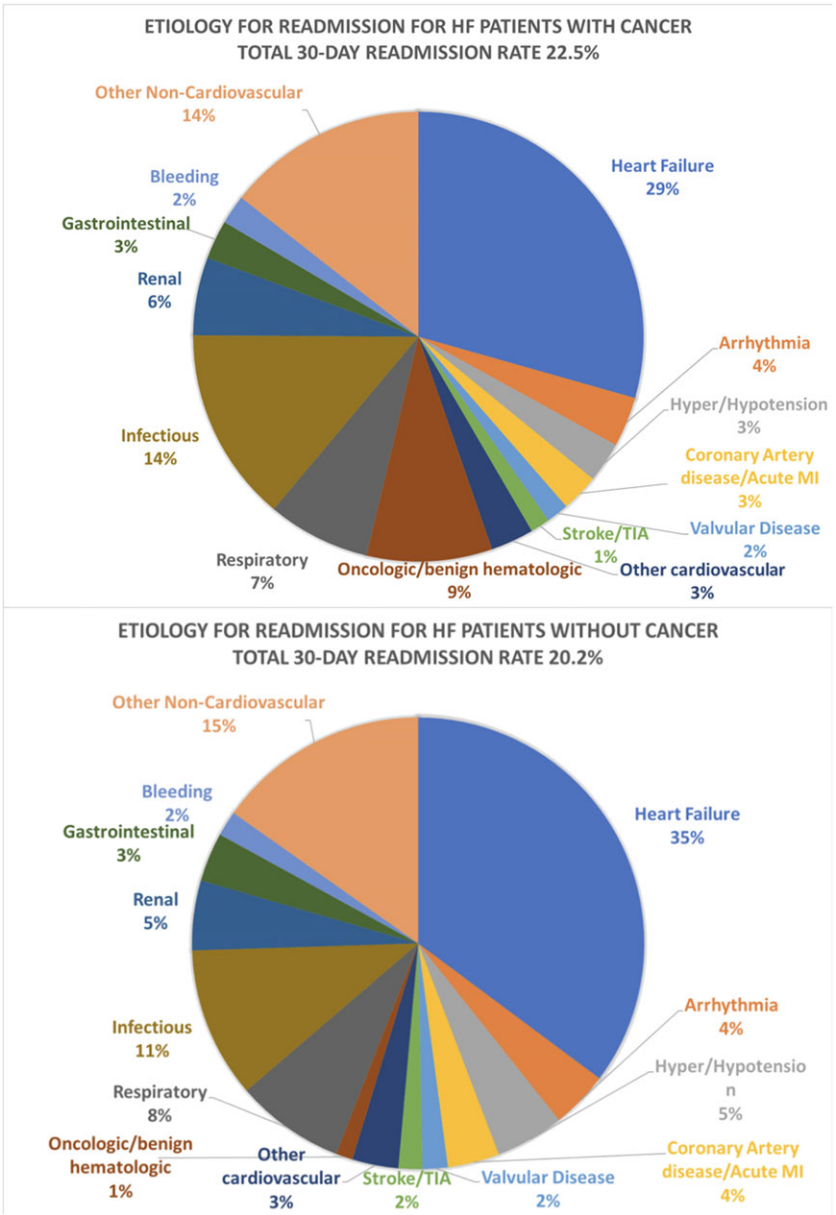
Figure 4 Thirty-day readmission in heart failure hospitalizations with cancer. Causes of 30 day readmission in heart failure hospitalizations with cancer and non-cancer (calculated annually and averaged for years 2013 and 2014). Patients with cancer saw higher 30 day overall readmission rates following index HF admission (22.5% vs. 20.2%, $P < 0.0001$). However, specific HF-related readmission rates were lower in those with cancer when compared with those without (29% vs. 35%, $P < 0.0001$).



Discussion

In this large, contemporary, population-based sample, we found that HF admission rates among cancer patients have increased over time, despite a concurrent decrease in HF admission rates in non-cancer patients. This observation was most evident among women and younger patients. Cancer patients with HF also had lower HF procedure use but longer lengths of stay, higher costs, and increased in-hospital mortality than had non-cancer patients, even after accounting for traditional risk factors and general mortality risk. Furthermore, patients with co-morbid cancer had higher subsequent 30 day readmission rates than had HF patients without cancer. However, non-HF-related causes were more frequent reasons for readmission after an index HF admission in the presence of cancer. These findings have important consequences given the rise in co-morbid cancer and HF prevalence, as well as the expanding focus on improved outcomes among patients presenting with HF.

Our study provides novel insights into hospital and patient-related factors, along with current practice patterns, that might underlie the disproportionate rise in HF admission rates among cancer patients. Specifically, the elevation in HF among those with cancer appeared independent of traditional risk factors, suggesting imputed risk associated with both cardiotoxic therapy exposure and the presence of cancer itself.[4] Notably, within this analysis, we observed an earlier increase in cancer patient HF admissions, precedent to the relative increase among those without cancer. A possible explanation for this observation may be the changing landscape of cancer therapeutics, moving away from cytotoxic chemotherapy to targeted therapies including monoclonal antibodies and tyrosine kinase inhibitors (TKIs).[4,5] For example, sunitinib, a TKI with anti-vascular endothelial growth factor (VEGF) activity has been associated with up to an 8% incidence of left ventricular dysfunction and HF development.[21] Trastuzumab, a monoclonal antibody used to treat HER2+ breast cancer is associated with a 2–28% rate of new left ventricular dysfunction,[22] with a 1.7–4.1% incidence of overt HF.[23]

Within this study, a general reduction in in-hospital HF mortality is in line with prior investigations among broad populations. However, the morality among those with concomitant cancer remained significantly higher, even after adjusting for traditional risk factors. While the exact reasons for the persistence of differentially elevated mortality rates in patients with both HF and cancer could not be ascertained owing to dataset limitations, plausible explanations can be made. For example, direct fibrotic injury after cancer-directed therapy may lead to limitations in cardiopulmonary reserve.[24–26] Alternatively, a primary focus on cancer treatment may inadvertently lead to more advanced HF presentations resulting from decreased awareness of the severity or aetiology of the cardiovascular issues.[27] Finally, patient and physician perceptions of both cancer prognosis and the benefits of HF treatments can affect timing of diagnosis. However, additional studies are needed to understand targetable factors underlying these differences.

Notably, we observed a disproportionately lower in-hospital HF-related procedure utilization rate among those with cancer, irrespective of co-morbid risk. This appears to have been driven by lower invasive procedure utilization. This may be directly related to the inherent or perceived risk of invasive assessments among patients with underlying cancer.[28] However, available data offer conflicting views on the safety of these procedures among lower-risk cancer patients.[29,30] Additionally, patients with cancer had higher 30 day readmission rates than had non-cancer patients; however, HF-related readmission rates were higher in the non-cancer cohort, when compared with cancer patients. This discrepancy is likely related to cancer-specific morbidities such as infection, anaemia, or thrombosis.[31]

There are several limitations of our study that warrant consideration. Because of reliance on *ICD-9-CM* codes, we were unable to determine the physician-perceived indication for hospital admission by specific cancer type. Moreover, patients with a diagnosis of metastatic cancer were excluded from our analyses, and while this may affect our data regarding overall health care utilization, we felt that physician perceptions about this subset of patients would adversely bias our results. We also could not determine the duration of a particular cancer diagnosis or specific cancer treatments. Therefore, the impact of specific cancer treatments such as TKIs, anthracyclines, or immune checkpoint inhibitors on HF hospitalization trends could not be reported. Also, data regarding cause of death and procedure utilization are not consistently recorded in the NIS, which makes it difficult to determine whether patients died as a result of an underlying illness or from a complication of HF. Although we used a propensity-score-matched design to account for indication bias, important unmeasured clinical characteristics that may be predictors of outcomes were not available, and therefore, these findings may be subject to confounding. Despite propensity-score matching, we could not account for unmeasured factors like patient care preference, (non-cancer) physician perception of prognosis, and shared decision making on the delivery of care. We also acknowledge that the in-house mortality can in part be just a result of higher hospitalization rates in cancer patients. In addition, owing to the administrative nature of data, we were unable to distinguish co-morbidities from complications of hospitalization. Finally, it is not possible to track patients after discharge in NIS, as readmissions are counted as separate admissions. However, the burden of HF hospitalizations was assessed in the NIS using established methodology and correlates with resource utilization in HF, regardless of the ability to longitudinally follow up individual patients.[14–16] Similar limitations also apply to NRD, although those patients were able to be tracked over the calendar year; however, we acknowledge that non-HF-related causes could be responsible for readmission after an index HF admission in the presence of cancer.

Conclusions

Heart failure-related admissions are on the rise among cancer patients, including in women and younger populations. Cancer patients with HF see lower resource utilization rates, lower rates of advanced HF care, and higher in-hospital morality than do those without cancer, even after accounting for overall risk. Further research into the factors related to these differences, such as the role of patient–physician prognosis perception and differential mechanisms or presentations of HF with novel cancer therapies, are needed.

Clinical perspectives

Competency in medical knowledge

Despite recent improvements in cancer outcomes, cancer patients presenting with HF continue to see lower cardiac procedure utilization rates but higher hospitalization costs, raised in-hospital mortality, and greater general readmissions rates.

Translational outlook

Additional studies are needed to understand the factors underlying the delivery of HF care in the presence of a cancer diagnosis.

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Conflict of interest

M.G.F. reports a consulting/advisory board relationship with Novartis Pharmaceuticals. D.A. is supported by NIH grant number K12-CA133250. All other authors declare no conflicts of interests in relation to the work presented in this manuscript.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Flow chart showing methods.
Figure S2. (A) Trends in HF hospitalization in males. (B) Trends in HF hospitalization in patients with age $<$ 50 years. (C) Incidence HF with breast cancer, lung cancer, colon cancer, prostate cancer and lymphoma. (D) Incidence HF in cancer with metastatic disease when compared to cancer patients without metastatic disease. (E) Incidence HF in cancer with metastatic disease when compared to non-cancer.
Figure S3. In-hospital mortality rates of HF with breast cancer, lung cancer, colon cancer, prostate cancer and lymphoma.
Figure S4. (A) Echocardiography Utilization in HF hospitalizations with cancer and non-cancer. (B) Cardiac Catheterization Utilization in HF hospitalizations with cancer and non-cancer. (C) Percutaneous Coronary Intervention Utilization in HF hospitalizations with cancer and non-cancer. (D) Mechanical Ventilation utilization in HF hospitalizations with cancer and non-cancer. (E)Inotrope Utilization in HF hospitalizations with cancer and non-cancer (Only data past 2005 is available with gross underreporting). (F) Mechanical Circulatory Support Utilization in HF hospitalizations with cancer and non-cancer. (G) Automated Cardioverter-Defibrillator Utilization in HF hospitalizations with cancer and non-cancer.
Table S1. Procedure ICD-9 CM and PRCCS codes.

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