ORIGINAL ARTICLE

Stress cardiomyopathy in hospitalized patients with cancer: machine learning analysis by primary malignancy type

Awad I. Javaid[1]* iD, Dominique J. Monlezun[2,3] iD, Gloria Iliescu[2], Phi Tran[4], Alexandru Filipescu[5], Nicolas Palaskas[2], Juan Lopez-Mattei[2], Saamir Hassan[2], Peter Kim[2], Mohammad Madjid[4], Mehmet Cilingiroglu[2], Konstantinos Charitakis[4], Konstantinos Marmagkiolis[2], Cezar Iliescu[2] iD and Efstratios Koutroumpakis[4]

[1]*Division of Cardiovascular Medicine, Kirk Kerkorian School of Medicine at the University of Nevada Las Vegas, 1701 W Charleston Blvd, Las Vegas, NV, USA;* [2]*Department of Cardiology, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA;* [3]*Center for Artificial Intelligence and Health Equities, Global System Analytics & Structures, New Orleans, LA, USA;* [4]*Division of Cardiology, The University of Texas Health Sciences Center at Houston, Houston, TX, USA; and* [5]*Department of Obstetrics and Gynecology, "Elias" Emergency University Hospital, Bucharest, Romania*

Abstract

Aims Previous studies have shown that patients with stress (Takotsubo) cardiomyopathy (SC) and cancer have higher in-hospital mortality than patients with SC alone. No studies have examined outcomes in patients with active cancer and SC compared to patients with active cancer without SC. We aimed to assess the potential association between primary malignancy type and SC and their shared interaction with inpatient mortality.

Methods and results We analysed SC by primary malignancy type with propensity score adjusted multivariable regression and machine learning analysis using the 2016 United States National Inpatient Sample. Of 30 195 722 adult hospitalized patients, 4 719 591 had active cancer, of whom 568 239 had SC. The mean age of patients with cancer and SC was 69.1, of which 74.7% were women. Among patients with cancer, those with SC were more likely to be female and have white race, Medicare insurance, hypertension, heart failure with reduced ejection fraction, obesity, cerebrovascular disease, anaemia, and chronic obstructive pulmonary disease ($P < 0.003$ for all). In machine learning-augmented, propensity score multivariable regression adjusted for age, race, and income, only lung cancer [OR 1.25; 95% CI: 1.08–1.46; $P = 0.003$] and breast cancer [OR 1.81; 95% CI: 1.62–2.02; $P < 0.001$] were associated with a significantly increased likelihood of SC. Neither SC alone nor having both SC and cancer was significantly associated with in-hospital mortality. The presence of concomitant SC and breast cancer was significantly associated with reduced mortality (OR 0.48; 95% CI: 0.25–0.94; $P = 0.032$).

Conclusions This analysis demonstrates that primary malignancy type influences the likelihood of developing SC. Further studies will be necessary to delineate characteristics in patients with lung cancer and breast cancer which contribute to development of SC. Additional investigation should confirm lower mortality in patients with SC and breast cancer and determine possible explanations and protective factors.

Introduction

Although cardiovascular disease and cancer remain the top two causes of death worldwide, novel therapeutic interventions have resulted in a decreased mortality rate in both groups. As a result of the increased recognition and earlier detection of cancer and simultaneous improvement of cardiac catheterization techniques, there has been a

heightened awareness of patients with cancer experiencing Takotsubo, or stress cardiomyopathy (SC).[1,2] These patients experience a unique clinical course in which the physical and emotional stress of cancer is compounded by the external stress of treatments such as surgery, chemotherapy, immunotherapy, and radiotherapy, in addition to the possible presence of internal paraneoplastic syndromes. Previous studies have shown that SC in patients with cancer is associated with higher odds of in-hospital mortality and long-term mortality when compared with patients with SC alone.[1,2] However, no studies have focused on the differences between patients with active cancer and SC versus patients with active cancer without SC. The association of SC with certain types of cancer and the factors predisposing patients with cancer and SC to higher mortality rates have not been well-studied. In an effort to resolve this gap in the literature, we used a large, public U.S. database of hospitalized patients to analyse demographics, clinical outcomes, and mortality stratified by specific cancer in patients with cancer and SC. Our aim was to explore the unique impact that a diagnosis of SC has on patients with specific types of cancer, so that clinicians may recognize these phenomena and hopefully reduce the morbidity associated with these diseases.

Methods

Data source

The data source for this study was the 2016 National Inpatient Sample (NIS) for hospital discharges. The NIS is the largest all-payer inpatient dataset in the USA and is sponsored by the US Department of Health and Human Services Agency for Healthcare Research and Quality and maintained within the Healthcare Cost and Utilization Project (HCUP). In 2016, NIS data coding adopted the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10). The NIS currently accounts for approximately 1 in 5 discharges from all community hospitals in the USA. The sampling strategy has been modified in the most recent data to reduce sampling bias and produce results more generalizable to all inpatient discharges in the country. This study used de-identified data and was therefore exempt from the M.D. Anderson Institutional Review Board review. The investigation conforms with the principles outlined in the Declaration of Helsinki.

Study design

We performed a nationally representative multicentre analysis of inpatient mortality by SC and primary malignancy, including overall and comparatively by primary organ site. The 2016 NIS dataset was selected because it is the first edition using ICD-10 codes and thus reflects current clinical trends. Study inclusion criteria included all NIS hospitalizations for adults aged 18 years or older during 2016. ICD-10 codes were used to identify demographics, co-morbidities, and outcomes. HCUP tools such as the Clinical Classification Software, which had been used prior to the NIS 2016 dataset for such purposes as classifying cancer, were not used in this study because they were found by HCUP as a beta version to be unreliable when applied to the 2016 dataset's ICD-10 data.

Statistical analysis

Descriptive statistics for demographics and co-morbidities were performed for the full sample. Co-morbidities were selected for analysis based on clinical and statistical significance in terms of existing literature. The co-morbidities included in this study were diabetes, hypertension, peripheral vascular disease, hyperlipidaemia, smoking, obesity, stroke, heart failure with reduced ejection fraction (HFrEF), cardiac arrest, human immunodeficiency virus (HIV), alcohol abuse, anaemia, chronic obstructive pulmonary disease (COPD), coagulopathy, chronic kidney disease (CKD), end stage renal disease (ESRD), and malignancy (overall and by primary malignancy type).

Bivariable analysis was then conducted among all patients according to the presence of SC (yes/no) and then among patients with active cancer and SC (yes/no). For continuous variables, independent sample t-tests were performed to compare means and Wilcoxon rank-sum tests were performed for medians. For categorical variables, Pearson's χ^2 tests or Fisher exact tests were performed to compare proportions. Variables found to be statistically significant in the bivariable analysis were then included in forward and backward stepwise regression to augment decision-making on which variables should be included in the final multivariable regression models. This regression analysis was conducted to assess the following outcomes: presence of SC and inpatient mortality. The regression models separately assessed these outcomes according to the following major predictors: malignancy, any type (yes/no), and primary malignancy each by specific type, including brain and nervous system, head or neck, thyroid, breast, lung, oesophagus, stomach, pancreas, liver or bile system, rectum or anus, colon, peritoneum, bone or connective tissue system, Hodgkin lymphoma, non-Hodgkin lymphoma, leukaemia, multiple myeloma, skin, uterus, cervix, ovarian, prostate, testes, bladder, and renal. These models featured the interaction between SC and malignancy when the outcome tested was mortality, while controlling for age, race, income, and mortality risk by diagnosis related group (DRG). Other variables were excluded based upon the below machine learning analysis and

diagnostic testing to produce the most clinically and statistically justifiable models.

Next, machine learning backed propensity score–adjusted multivariable regression was conducted for mortality and controlled for age, race, income, and mortality risk by DRG in addition to the likelihood of undergoing percutaneous coronary intervention (PCI) and the NIS weights accounting for the cluster sample data structure. The propensity score was created for the likelihood of undergoing PCI (the treatment), balance was confirmed among blocks, and then the propensity score was included in the final regression models as an adjusted variable. This causal inference approach (propensity score adjustment) was chosen because it is a widely accepted method to reduce selection bias and the effect of confounding variables. Competing causal inference approaches such as fixed, random, and mixed effects were not appropriate, because the dataset lacked adequate repeated hospitalizations from the same subjects. Propensity score adjustment was used rather than covariate adjustment without propensity score, in order to be able to test interactions and higher order terms to produce the most robust estimated probability of treatment assignment. Finally, propensity score adjustment rather than competing propensity score techniques was used because of its superior performance in the appropriate context, confirmed by current statistical theory and adequate diagnostic quantitative testing of the final models in cardiovascular studies.[3,4]

The utility of this above hybrid analytic approach, which integrates the traditional statistical method of frequentist-based multivariable regression (supported by propensity score-based causal inference analysis) and supervised learning-based machine learning has been previously demonstrated. In this approach, causal inference results which are more familiar to medical science audiences can be confirmed and replicated automatically through machine learning, while producing more rapid and accurate results compared with traditional statistics.[5–9]

To modify the final models until optimal performance was achieved, performance was first assessed relative to results from backward propagation neural network machine

Table 1 Characteristics of patients with cancer and stress cardiomyopathy

Characteristic	All hospitalizations	Patients with cancer	Patients with cancer and SC	*P* value
Demographics				
Age, years, mean ± SD	57.51 ± 20.33	65.07	69.09	<0.001
Female	58.15	48.86	74.76	<0.001
Race				
White	67.79	71.07	80.45	<0.001
Black	15.14	13.49	8.64	<0.001
Hispanic	15.14	8.75	3.91	<0.001
Asian	2.69	3.16	3.50	<0.001
Native American	0.62	0.45	0.21	<0.001
Other	2.93	3.08	3.29	
Insurance				
All groups				<0.001
Commercial	27.63	28.46	22.33	
Medicare	46.92	55.29	69.13	
Medicaid	18.62	11.63	6.41	
VA	2.95	2.60	1.17	
None	3.88	2.03	0.97	
Medical history				
Diabetes	18.88	19.14	15.31	<0.027
Hypertension	54.33	58.05	64.73	0.002
Hyperlipidaemia	31.49	31.83	41.09	<0.001
Obesity	14.57	10.30	5.04	<0.001
CVA/TIA	4.29	3.06	5.43	0.002
HFrEF	2.54	2.25	8.53	<0.001
Cardiac arrest	0.79	0.90	3.29	<0.001
Smoking	2.23	1.23	0.58	0.183
HIV	0.40	0.55	0.00	0.091
Anaemia	20.36	36.20	43.99	0.001
Thrombocytopenia	4.54	8.94	10.66	0.171
COPD	16.32	19.15	29.26	<0.001
Coagulation disorder	6.26	11.51	15.50	0.004
Cirrhosis	2.27	3.00	3.68	0.361
CKD 3–5	11.35	10.25	11.43	0.377
ESRD	3.58	2.33	2.33	0.992

Except age, all numbers are percentages.
CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; ESRD, end stage renal disease; HFrEF, heart failure with reduced ejection fraction; HIV, human immunodeficiency virus; SD, standard deviation; TIA, transient ischaemic attack; VA, veterans affairs.

learning to ensure comparability by root mean squared error and accuracy. Regression model performance was additionally assessed with correlation matrix, area under the curve, Hosmer–Lemeshow goodness-of-fit test, Akaike and Schwarz Bayesian information criterion, variance inflation factor, and tolerance, multicollinearity, and specification error. An academic physician-data scientist and biostatistician confirmed that the final regression results were sufficiently supported by the existing literature and clinical and statistical theory. Fully adjusted regression results were reported with 95% confidence intervals (CIs) with statistical significance set at a 2-tailed P-value of <0.05. Statistical analysis was performed with STATA 14.2 (STATA Corp, College Station, Texas, USA), and machine learning analysis was performed with Java 9 (Oracle, Redwood Chores, California, USA).

Results

Of 30 195 722 adults admitted to US hospitals in 2016, 4 719 591 (15.6%) had active cancer, of whom 568 239 (12.0%) had SC. Baseline demographics are outlined in *Table 1*. Among patients with active cancer, those with SC were more likely to be female (74.7% vs. 48.8%, $P < 0.001$), white

Table 2 Machine learning-augmented propensity score-adjusted multivariable regression among all adult hospitalizations

Outcome	Predictor of outcome	Odds ratio with 95% CI	P value
SC	Cancer	1.05 (0.98–1.12)	0.185
	Metastatic cancer	0.94 (0.82–1.08)	0.398
	Breast cancer	1.81 (1.62–2.02)	<0.001
	Lung cancer	1.25 (1.08–1.46)	0.003
	Skin cancer	0.92 (0.78–1.08)	0.298
	Colon cancer	1.02 (0.85–1.22)	0.823
	Leukaemia	1.17 (0.93–1.47)	0.171
Mortality	SC	0.93 (0.82–1.05)	0.216
	SC with cancer	0.92 (0.71–1.19)	0.523
	SC with metastatic cancer	0.75 (0.49–1.15)	0.191
	SC with breast cancer	0.48 (0.25–0.94)	0.032
	SC with lung cancer	0.97 (0.58–1.59)	0.895
	SC with skin cancer	1.57 (0.72–3.40)	0.256
	SC with colon cancer	0.80 (0.37–1.73)	0.579
	SC with leukaemia	0.92 (0.41–2.04)	0.831

CI, confidence interval; SC, stress cardiomyopathy.

Figure 1 Prevalence (percentage) of primary malignancy status by stress cardiomyopathy among malignancies with highest stress cardiomyopathy prevalence. *Statistically significant versus not, $P < 0.05$. The primary malignancies with the highest proportion or prevalence of SC within each primary are represented in *Figure 1*, which demonstrates that SC was generally more prevalent for patients with historical rather than active disease and metastatic rather than non-metastatic disease.
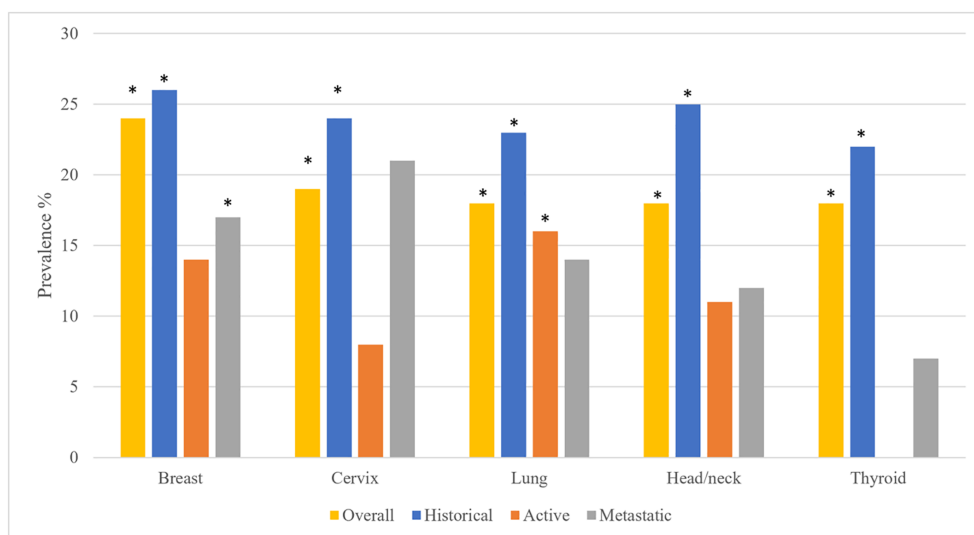
Figure 2 Graphic depicting central findings. This illustration demonstrates the key findings of our analysis.
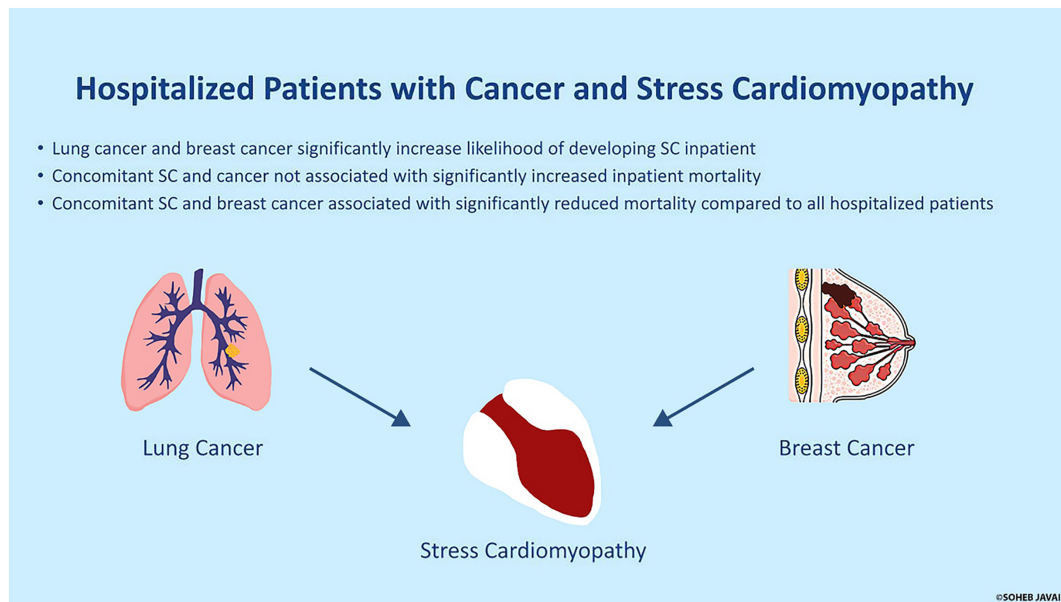
(80.4% vs. 71.0%, *P* < 0.001), and have Medicare as insurance (69.1% vs. 55.2%, *P* < 0.001) compared with patients without SC. Patients with active cancer and SC were more likely to have a history of hypertension (64.7% vs. 58.0%, *P* = 0.002), hyperlipidaemia (41.09% vs. 31.83%, *P* < 0.001), HFrEF (2.2% vs. 8.5%, *P* < 0.001), obesity (10.3% vs. 5.0%, *P* < 0.001), cerebrovascular accident and/or transient ischaemic attack (5.4% vs. 3.0%, *P* = 0.002), anaemia (43.9% vs. 36.2%, *P* < 0.001), coagulation disorder (15.5% vs. 11.5%, *P* = 0.004), cardiac arrest (3.3% vs. 0.9%, *P* < 0.001), and COPD (29.3% vs. 19.2%), compared with those with cancer without SC. In patients with active cancer, patients with SC were less likely to have a history of diabetes mellitus (15.3% vs. 19.1%, *P* < 0.027) compared with those without SC. There were no significant differences between the two groups in terms of history of smoking, CKD, ESRD, HIV, and cirrhosis. The five most common primary malignancies in patients with SC were breast (13.3%), lung (10.2%), skin (9.5%), colon (8.0%) cancer, and leukaemia (4.7%) (*Table 2*). The primary malignancies with the highest proportion of SC within each primary are represented in *Figure 1*.

Among all adult hospitalized patients in propensity score adjusted multivariable regression analysis controlling for age, race, income, mortality risk by NIS-calculated diagnosis-related group, and likelihood of undergoing PCI, the only primary malignancies that significantly increased the likelihood of SC were lung cancer [odds ratio (OR) 1.25; 95% CI (confidence interval): 1.08–1.46; *P* = 0.003] and breast cancer [OR 1.81; 95% CI: 1.62–2.02; *P* < 0.001] (*Table 2*) (*Figure 2*). Neither a diagnosis of cancer [OR 1.05; 95% CI: 0.98–1.12; *P* = 0.185] nor metastatic cancer [OR 0.75; 95% CI: 0.49–

1.15; *P* = 0.398] was significantly associated with the presence of SC. In separate regression, neither the presence of SC, nor SC with cancer, nor SC with metastatic cancer was significantly associated with mortality (*Table 2*). The concomitant diagnosis of SC and breast cancer, in contrast to other primary malignancies, was associated with significantly reduced mortality (OR 0.48; 95% CI: 0.25–0.94; *P* = 0.032) compared with patients without SC or breast cancer (*Table 2*).

Discussion

There is a paucity of data in patients with SC and cancer. Although previous studies have evaluated patients with SC versus patients with SC and cancer, ours is the first to our knowledge, to analyse patients with cancer and SC versus patients with cancer and no SC. In addition, previous studies have not assessed specific cancer types in patients with SC. In our study, we placed special focus on patients with cancer in general, from the perspective of internists, cardiologists, and oncologists who regularly encounter a patient population with malignancy. Despite our specific focus, we were still able to demonstrate significant findings related to previous studies.

Several important findings were observed in our analysis of more than 500 000 patients with active cancer and SC. First, SC is relatively common in patients with cancer, affecting more than 1 in every 10 patients. Certain demographic groups in hospitalized patients with cancer

disproportionately developed SC, including women, white patients, and those with Medicare as insurance. Specific conditions in the medical history of patients with cancer contributed to the development of SC, including hypertension, HFrEF, obesity, cerebrovascular disease, anaemia, coagulation disorder, cardiac arrest, and COPD. The five most common malignancies in this cohort were breast, lung, skin, and colon cancer, followed by leukaemia. SC was generally more prevalent for patients with historical rather than active disease and metastatic rather than non-metastatic disease. Cancers, in general, did not increase the likelihood of developing SC in the hospital, while lung cancer and breast cancer did. Lastly, having SC and cancer generally was not associated with in-hospital mortality, regardless of cancer type, and having breast cancer with SC reduced the likelihood of mortality.

The term Takotsubo cardiomyopathy initially appeared in the literature in 1990, although similar descriptions of this disease state were previously described.[10] Studies have shown an increase in incidence and hospitalization for SC over time,[11,12] which is likely due to improved recognition of the disease and greater availability of coronary angiography. Concurrently, with advancements in research, there has been a rapid development of new drugs and treatment regimens for cancer. In the USA from 2010 to 2018, 27% of all new FDA drug approvals were for cancer.[13] In 2020 alone, at least 20 new cancer drugs were approved for use as a new agent or for a new indication.[14] Immunotherapy, radiotherapy, and chemotherapy continue to rapidly evolve every year.[15–17] These novel therapies have contributed toward a consistently declining mortality rate in multiple types of cancer.[18] The increase in diagnosis of SC, coupled with the decreasing mortality rate in cancer has led to greater interest in patients with cancer experiencing SC. Although newer therapies have been beneficial for patients with cancer, many of them have been implicated in causing SC. Several drugs have been cited, most commonly 5-fluorouracil.[19] Others include bevacizumab, capecitabine, combretastatin, rituximab, tyrosine kinase inhibitors, vascular endothelial growth factor inhibitors, other angiogenesis inhibitors, and taxols.[19] Case reports have shown an association between radiotherapy and SC.[20,21] A study of hospitalized patients from 2007 to 2014 showed that patients with prior intrathoracic or mediastinal cancer and radiation therapy had higher odds of hospitalization and in-hospital mortality in admissions for SC.[22]

Stress cardiomyopathy and cancer share many risk factors, and this was confirmed in our analysis. In our cohort of patients with cancer, anaemia was significantly higher in patients with SC. Anaemia is a common finding in patients with cancer which occurs due to chronic inflammation, as well as the toxic effect of various treatment modalities, which can damage red blood cells. Greater than 30% of patients present with cancer-related anaemia even before starting antineoplastic treatments, and this number rises to approximately 67% once treatment is initiated.[23] In patients with cancer, anaemia is associated with a lower quality of life.[24] A recent analysis of hospitalized patients from 2016 to 2018 showed that in patients with SC, anaemia was associated with worse outcomes compared with patients without anaemia.[25] Patients with both SC and anaemia had significantly higher rates of cardiogenic shock, ventricular arrhythmia, acute kidney injury, acute respiratory failure, as well as longer length of hospital stay, and higher total charges.[25] Our results, in conjunction with other studies, demonstrate that anaemia is a significant finding in patients with cancer and should be viewed as a strong risk factor for SC.

Stress cardiomyopathy is predominantly prevalent in older women,[26,27] partly due to increased sympathetic drive and endothelial dysfunction in this population, which predisposes to microvascular dysfunction.[28] Additionally, increased oxidative stress, greater anxiety, depression, and sleep disturbances may play a role.[28] These same risk factors are shared by patients with malignancy due to the mental and physical stress associated with the diagnosis itself as well as the related treatments. In our cohort, the average age of patients with cancer and SC was 69 and the percentage of women was 74.7%, while the group of those with cancer without SC had an average age of 65, with women accounting for 48.9%.

Recent large cohorts have shown that SC is significantly more prevalent in white patients compared with patients of other races, which is also true of our co.[2,29] A greater proportion of patients with SC and cancer in our study were also found to have Medicare insurance, which is intuitively logical, as SC tends to affect older patients.[29] In our cohort, patients with cancer and SC had a lower prevalence of diabetes mellitus, smoking, CKD, ESRD, and HIV compared with those without SC. There has been conflicting evidence regarding the prevalence of diabetes in SC. In one review of 959 studies with 33 894 patients, diabetes was found to be much less prevalent in SC when compared with national data on diabetes.[30] In another recent study, the prevalence was found to be higher than expected when controlled for age and sex.[31]

Chronic obstructive pulmonary disease is not classically discussed as linked with SC; however, recent evidence is demonstrating an association. A NIS analysis of 3129 patients hospitalized for SC from 2016 to 2017 showed that patients with concomitant COPD had higher rates of inpatient mortality, acute respiratory failure, cardiogenic shock, longer length of stay, and higher charges of stay.[32] At the same time, many patients with lung cancer suffer from COPD due to the shared risk factor of smoking. Elevated catecholamine levels have been known to play a role in development of SC.[33] The common use of beta agonists by COPD patients may also explain the elevated prevalence of SC in our cohort of patients with SC and cancer.

Stress cardiomyopathy was far more prevalent in our study in patients with historical, rather than active disease. This

could possibly be due to multiple stressors of accumulated therapy over time. The finding that SC was more prevalent in metastatic disease is expected, considering the mental and physical burden that this diagnosis incurs. These findings are an important guide to clinicians in terms of determining which patients are more likely to suffer from SC when they are admitted to the hospital.

A noteworthy finding in our study was that, despite all the related treatments known to cause physical and emotional stress and cardiotoxicity, the only malignancies significantly associated with developing SC were breast and lung cancer. Anthracyclines and anti-HER2 therapies for breast cancer are notorious for causing cardiotoxicity. SC has long been known to preferentially affect postmenopausal women and evidence shows that the association in this population may be due to oestrogen deprivation.[33] Patients with breast cancer often undergo anti-oestrogen therapy, which can lead to decreased oestrogen levels. Additionally, breast cancer is most prevalent in older women. These factors may explain the association with SC in our cohort. Most literature regarding lung cancer in SC involves case reports in the setting of cardiotoxic therapies. Further investigation will be necessary to establish a possible link between lung cancer and SC and determine why other malignancies did not increase the odds of developing SC.

In our analysis, the presence of concomitant SC and cancer was not associated with increased in-hospital mortality when compared with all other hospitalized patients. Although this specific comparison has not been studied in a large cohort, the finding contrasts significantly with previous studies in patients with SC. In a 2019 study of 1604 patients from the International Takotsubo Registry, malignancy was observed in 267 patients (16.6%).[1] Patients with SC and malignancy had a higher in-hospital mortality (6.7% vs. 3.4%, P = 0.010) when compared with SC patients without malignancy. Long-term mortality was higher in patients with malignancy over a period of 5 years ($P < 0.001$), while 30-day mortality did not differ significantly (P = 0.17). A large study of outcomes in hospitalized patients with SC from 2007 to 2013 identified 122 855 adults with SC, of which 8089 had cancer (6.6%). In this cohort, in-hospital mortality in SC patients with cancer was significantly higher when compared with SC patients without cancer (12.8 vs. 3.8, $P < 0.050$).

In our study, breast cancer in the setting of SC was associated with significantly reduced mortality when compared with all hospitalized patients. This finding is consistent with trends in patients with breast cancer and cardiovascular disease found in previous studies. A large study of NIS patients in 2018 showed that the diagnosis of breast cancer in patients undergoing PCI was not significantly associated with either in-hospital mortality or any of the complications studied.[34] A more recent 2021 study showed that women with breast cancer developing heart failure (HF) after trastuzumab-based chemotherapy had a lower risk of HF

hospital presentations than patients with HF and no cancer.[35] This result was likely driven by the fact that the cohort of patients with breast cancer had fewer co-morbidities despite a diagnosis of malignancy. Moreover, in our study, in patients with breast cancer and SC, a historical diagnosis of breast cancer was far more prevalent than a diagnosis of active cancer (*Figure 1*). Therefore, the likely explanation for patients with SC and breast cancer having reduced mortality, is that these patients have fewer co-morbidities and are generally less frail compared with other hospitalized patients, especially those undergoing ongoing treatment for cancer.

Additional data over a span of multiple years will be necessary to verify results and identify trends. As long-term follow-up cannot be assessed in the NIS sample, it is possible that patients in our cohort may have had increased mortality if their progress was followed post-discharge over a period of months to years. However, our findings remain valuable from the perspective of risk stratifying patients during inpatient admissions. Our findings require further investigation in longer prospective studies.

Limitations

The findings of our study should be interpreted within the context of certain limitations. The study is observational, retrospective, and not randomized and hence subject to selection bias and confounding factors. In NIS data, it is not possible to differentiate between the effect of presence of cancer versus specific cancer treatments. The stage and treatment of specific cancers are not available but are major determinants of mortality. Additionally, the administrative dataset design relies on user entry of ICD-10 coding which is susceptible to variability in diagnosis. This limitation is counterbalanced by our robust causal inference analysis, as well as the large number of subjects from multiple hospitals throughout the nation.

Conclusions

Among a large, nationally representative cohort of patients hospitalized with active cancer, SC was not associated with in-hospital mortality. SC was more prevalent in those with historical cancer compared with active cancer. In addition, patients with both SC and breast cancer had significantly reduced mortality when compared with all patients with cancer. Further controlled and prospective studies will be necessary to confirm these findings, evaluate trends over time, and determine the possible protective factors in patients with breast cancer and SC. Clinicians should be aware, early during hospitalization, of the increased likelihood of SC in patients with lung and breast cancer, historical versus

active disease, and metastatic versus non-metastatic disease, in order to reduce morbidity associated with these diagnoses.

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Conflict of interest

None declared.

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