Frequency of Takotsubo Cardiomyopathy in Adult Patients Receiving Chemotherapy (from a 5-Year Nationwide Inpatient Study)

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Takotsubo cardiomyopathy (TC) develops in patients who are under significant emotional, psychosocial, or sudden biochemical stress. However, the added burden of TC on the patients receiving chemotherapy has never been studied. We aimed to describe the additional clinical and economic burden, along with the potential predictors of TC and related in-hospital mortality in patients receiving chemotherapy using the largest inpatient cohort. We identified chemotherapy-related adult hospitalizations using the National Inpatient Sample databases (2010 to 2014). Primary end points were the incidence of TC and the odds of in-hospital mortality. Secondary end points were gender-based incidence differences, length of stay (LOS), hospital charges, and discharge disposition. We identified 1,067,977 chemotherapy-related hospitalizations, of which, 562 hospitalizations revealed TC incidence. Other co-morbidities were also significantly higher in the TC cohort. In unmatched analyses, the LOS (median 17 days vs 5 days) and total hospital charges (median $162,825 vs $46,335) were significantly higher in the TC group. A propensity-matched analysis confirmed the increased healthcare burden. Multivariate analysis revealed over 2-times higher odds (odds ratio [OR] 2.17) of in-hospital mortality in the TC group. Female gender (OR 2.48), and nonelective (OR 2.26), and nonfederal government hospital (OR 2.68) admissions had more than twice the odds of developing TC. An advanced age, Asian race, urban-teaching hospital, and complications such as septicemia, fluid-electrolyte disorders, cardiogenic shock, and respiratory failure independently raised mortality odds in the TC group. In conclusion, we observed an overall increasing nationwide trend in TC incidence in patients receiving chemotherapy, which adds to significantly increased in-hospital mortality, LOS, and healthcare charges. **(Am J Cardiol 2019;123:667−673)**

Takotsubo cardiomyopathy (TC) or broken heart syndrome is characterized by the abnormal apical dilatation of the heart albeit minimal to mild myocardial necrosis.[1] Several anatomical variants of TC have also been reported in the literature.[2] Clinically, TC presents as a milder yet similar form of an acute coronary syndrome, which is mainly characterized by the severe left ventricular dysfunction with apical ballooning, in the absence of obstructive coronary artery disease.[1,3,4] The annual incidence of TC in the United States has shown an increasing trend from 111 per million to 438 per million in the general population from 2007 to 2013.[5] Unfortunately, TC is associated with significant morbidity and mortality with an estimated in-hospital mortality rate ranging from 4.5% to 5.6%.[6,7] In addition to the commonly identified precipitating factors, cancer has also been believed to be a potential precipitating factor for the development of TC ranging from 4% to 29% of cases.[8−12] Furthermore, TC has been implicated as a paraneoplastic phenomenon.[13] In certain cancer patients, it has been suggested that chemotherapy itself may be a more likely culprit than cancer itself.[14] The objective of this retrospective study was to assess the incidence and predictors of TC while quantifying the associated healthcare burden and predictors of in-hospital mortality owing to TC in patients receiving chemotherapy.

Methods

We constructed our investigation from the largest in-hospital database, the National Inpatient Sample (NIS), from January 2010 to December 2014. It is a part of the

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Healthcare Cost and Utilization Project supported by the Agency for Healthcare Research and Quality and incorporates released information from 20% of inpatient discharges of all nonfederal US hospital facilities (excluding rehabilitation and long-term acute care hospitals), representative of 95% of all community hospitals excluding rehabilitation and long-term hospitals.[15]

All chemotherapy-related adult hospitalizations were identified by applying the International Classification of Diseases, Ninth Revision; Clinical Modification codes V58.1x (encounter for chemotherapy and immunotherapy for neoplastic conditions), V66.2x (convalescence and palliative care after chemotherapy), V67.2x (follow-up examination after chemotherapy), E93.07 (body measurement), and the procedure code of 99.25 for the injection or infusion of cancer chemotherapeutic agents. We then stratified the chemotherapy population into 2 cohorts using the International Classification of Diseases, Ninth Revision; Clinical Modification code 429.83 for TC. We excluded patients with a primary discharge diagnosis of the acute coronary syndrome to minimize selection bias.

The primary outcomes of interest were (1) burden of TC in the hospitalized patients who underwent chemotherapy and (2) incidence and odds of in-hospital mortality related to TC. The secondary outcomes were defined as; discharge disposition, length of stay (LOS), total hospital charges, and gender differences in both the groups. We further distinguished patient and hospital-level variables as well as in-hospital outcomes including their co-morbidities in our prespecified patient cohorts, which compared patients who underwent chemotherapy with TC versus those without. Our study did not require an institutional review board approval as the NIS is an openly accessible database containing de-identified information.

The discharge weights were incorporated into the analysis to generate the national estimates. We utilized the Pearson's chi-square test for categorical and Student's *t* test for the continuous variables to contrast the baseline attributes in both groups. We developed a 2-step hierarchical multivariate logistic regression model to evaluate for the patient- and hospital-level components, co-morbidities, and in-hospital outcomes related to TC. Patients with missing information were excluded from the analysis. The threshold level of clinical significance (alpha) was set at 5%. The propensity-score-matched analysis was performed with a ratio of 1:1 without replacement using caliper scale of 0.1. Predictors of in-hospital mortality in the TC group were assessed using a multivariable logistic regression model. The statistical analyses were performed utilizing SPSS Statistics 24 (IBM Corp., Armonk, New York).

Results

We identified a total of 1,067,977 chemotherapy-related hospitalizations, of which 562 admissions demonstrated TC on the same admission. The incidence estimates of TC in chemotherapy patients for each year from 2010 to 2014 are plotted in Figure 1**.** The mean overall incidence of TC was found to be 53.0 per 100,000 chemotherapy-related hospitalizations. The mean incidence of TC in the female and male patients was 37.0 per 100,000 and 16.6 per 100,000 chemotherapy-related hospitalizations, respectively. The incidence of TC in the female patients exceeded that of the male patients each year by a mean difference of 20.4 per 100,000 patients. When regression analysis was conducted, the overall annual incidence growth rate was demonstrated to be 8.6 per 100,000 patients.

Comparatively, the mean age of the TC group was significantly higher as demonstrated in Table 1 (mean age 63 vs 55 years). Female patients dominated the TC group, whereas men were more prevalent in the non-TC group. Overall, nonelective admissions comprised a significantly larger component in the TC group. No differences were evident among the ethnic composition of both groups.

Pre-existing co-morbidities were compared between the weighted population estimates presented in Table 1. The prevalence of other co-morbidities was significantly higher in the TC cohort. The presence of diabetes with and without complications, liver disease, and renal failure was not significantly different amongst both groups. There were considerably fewer obese patients in the TC cohort.

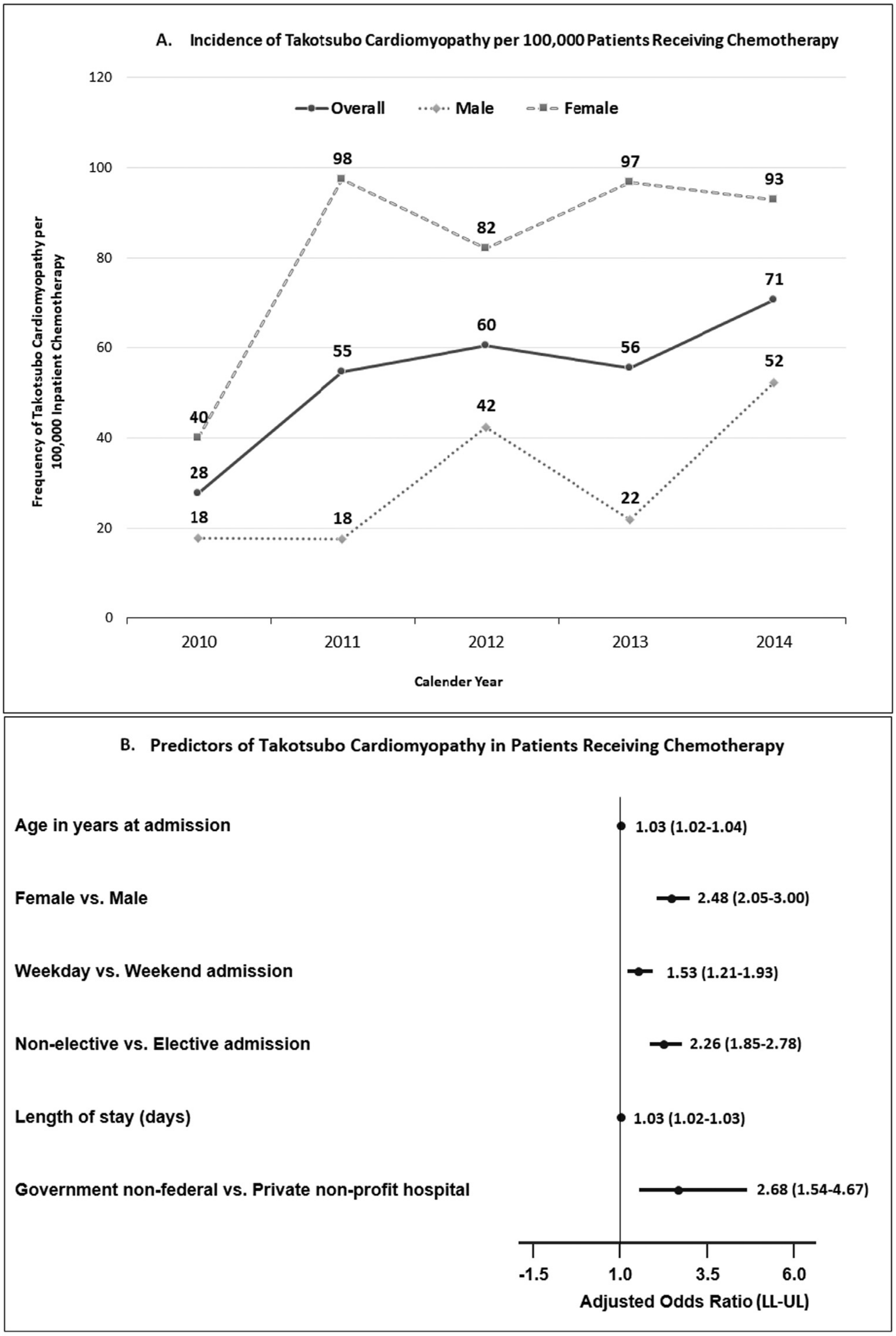
In unmatched analyses, all-cause in-hospital mortality, LOS, and total hospital charges were significantly higher in the TC group (Table 2A). The propensity-matched analysis reported similar findings in terms of higher all-cause in-hospital mortality (17.7% vs 1.0%, $p < 0.001$), LOS (17 vs 1 day, $p < 0.001$), and total hospital charges ($162,825 vs $7,600, $p < 0.001$) in the TC group (Table 2B). Over one-third of the TC patients followed a routine disposition whereas a considerably higher number of patients in the TC group was discharged with home health care or to other facilities delivering a similar level of care as compared with the non-TC group.

Multivariate analysis adjusted for age, gender, race, payer status, median household income, hospital characteristics, and co-morbidities showed more than 2 times higher odds (odds ratio [OR] 2.17, 95% confidence interval [CI] 1.68 to 2.80, $p < 0.001$) of in-hospital mortality in patients who developed TC. Nonfederal government hospitals (OR 2.68), nonelective (OR 2.26) admissions, and the female gender (OR 2.48) were found to have more than twice the odds of developing TC (Figure 1).

Univariate logistic regression analysis revealed a number of factors, which predicted in-hospital mortality in patients receiving chemotherapy who developed TC (Table 3). An advanced age (≥85 years) and Asian/Pacific Islander race predicted higher in-hospital mortality. Interestingly, African-American race had a lower odds of mortality. Prolonged LOS marginally raised the odds of mortality. Urban teaching hospital admissions and private insurance status were associated with higher odds of in-hospital mortality. Septicemia, fluid-electrolyte disorders, cardiogenic shock, and respiratory failure were top independent predictors of in-hospital mortality in the TC group. Overall, the mortality odds in TC hospitalizations were higher, a trend which has decreased from 2011 to 2014 (OR 6.27 vs 2.85).

Discussion

Our study provides the first attempt at quantifying the additional burden related to the occurrence of TC in the



*Multivariate model was adjusted for age, sex, race, payer status, median household income, hospital characteristics. †LL=lower level, UL=Upper level. *P* <0.05 was considered clinically significant.

Figure 1. Incidence and predictors of takotsubo cardiomyopathy in patients receiving chemotherapy. (*A*) The incidence of takotsubo cardiomyopathy per 100,000 chemotherapy-related hospitalizations in the United States: The overall mean incidence of takotsubo cardiomyopathy was found to be 53.0 per 100,000 chemotherapy-related hospitalizations. The mean incidence of takotsubo cardiomyopathy in the female and male patients was 37.0 per 100,000 and 16.6 per 100,000 chemotherapy-related hospitalizations, respectively. The incidence of takotsubo cardiomyopathy in the female patients exceeded that of the male patients each year by a mean difference of 20.4 per 100,000. (*B*) Predictors of takotsubo cardiomyopathy in patients receiving chemotherapy: nonelective (OR 2.26), Weekday (OR 1.53), nonfederal government hospital (OR 2.68) admissions, and female gender (OR 2.48) were found to be strong predictors of takotsubo cardiomyopathy development. Age (OR 1.03) in years at admission and length of stay (OR 1.03) were not strong predictors of takotsubo cardiomyopathy development.

Table 1
Baseline characteristics of study population receiving chemotherapy

Variables	Takotsubo cardiomyopathy		p value
	No (n = 1,067,415)	Yes (n = 562)	
Age (years) at admission			**<0.001**
Mean age ± SD	55.4±16.3	62.6±12.1	
18-44	246,747 (23.1%)	40 (7.1%)	
45-64	485,281 (45.5%)	266 (47.4%)	
65-84	319,228 (29.9%)	246 (43.8%)	
≥85	16,159 (1.5%)	<11 *	
Sex			**<0.001**
Male	583,776 (54.7%)	174 (30.9%)	
Female	483,476 (45.3%)	388 (69.1%)	
Admission day			**<0.001**
Monday-Friday	967,404 (90.6%)	470 (83.6%)	
Saturday-Sunday	100,002 (9.4%)	92 (16.4%)	
Type of admissions			**<0.001**
Non-elective	518,310 (48.7%)	405 (72.1%)	
Elective	545,463(51.3%)	157 (27.9%)	
Race			0.001
White	670,250 (67.3%)	363 (70.8%)	
Black	135,986 (13.6%)	76 (14.8%)	
Hispanic	118,185 (11.9%)	60 (11.6%)	
Asian or Pacific Islander	33,748 (3.4%)	15 (2.9%)	
Native American	3,661 (0.4%)	−	
Others	34,581 (3.5%)	−	
Primary expected payer			**<0.001**
Medicare	355,945 (33.4%)	285 (50.8%)	
Medicaid	180,122 (16.9%)	45 (8.0%)	
Private including HMO †	443,126 (41.6%)	197 (35.0%)	
Self − Pay/No charge/Other	85,956 (8.1%)	35 (6.1%)	
Bed size of hospital			**0.025**
Small	101,329 (9.5%)	62 (11.1%)	
Medium	175,141 (16.5%)	70 (12.4%)	
Large	785,535 (74.0%)	430 (76.5%)	
Location/teaching status of hospital			**<0.001**
Rural	30,828 (2.9%)	14 (2.5%)	
Urban − non-teaching	193,398 (18.2%)	59 (10.6%)	
Urban - teaching	837,779 (78.9%)	488 (86.9%)	
Region of hospital			0.057
Northeast	235,055 (22.0%)	131 (23.3%)	
Midwest	230,000 (21.5%)	140 (24.9%)	
South	405,578 (38.0%)	184 (32.8%)	
West	196,782 (18.4%)	106 (19.0%)	
Comorbidities			
Alcohol abuse	20,660 (1.9%)	20 (3.6%)	**0.005**
Deficiency anemias	242,900 (22.8%)	153 (27.2%)	**0.012**
Rheumatoid arthritis /Collagen vascular diseases	18,493 (1.7%)	25 (4.5%)	**<0.001**
Chronic blood loss anemia	7,371 (0.7%)	11 (1.9%)	**<0.001**
Congestive heart failure	45,080 (4.2%)	255 (45.4%)	**<0.001**
Chronic pulmonary disease	132,493 (12.4%)	124 (22.1%)	**<0.001**
Coagulopathy	136,499 (12.8%)	152 (27.1%)	**<0.001**
Depression	113,034 (10.6%)	85 (15.1%)	**<0.001**
Diabetes, uncomplicated	157,654 (14.8%)	78 (13.9%)	0.563
Diabetes with complications	20,356 (1.9%)	15 (2.6%)	0.187
Hypertension	421,855 (39.5%)	293 (52.2%)	**<0.001**
Hypothyroidism	88,648 (8.3%)	64 (11.4%)	**0.008**
Liver disease	40,332 (3.8%)	30 (5.3%)	0.053
Lymphoma	38,072 (3.6%)	69 (12.3%)	**<0.001**
Fluid and electrolyte disorders	290,265 (27.2%)	334 (59.5%)	**<0.001**
Metastatic cancer	91,713 (8.6%)	93 (16.7%)	**<0.001**
Other neurological disorders	47,086 (4.4%)	49 (8.8%)	**<0.001**
Obesity	64,807 (6.1%)	15 (2.7%)	**0.001**
Peripheral vascular disorders	22,988 (2.2%)	30 (5.3%)	**<0.001**
Renal failure	66,053 (6.2%)	45 (8.0%)	0.074
Valvular heart disease	23,486 (2.2%)	30 (5.3%)	**<0.001**

Significant p values <0.05 (bold values) at 95% confidence interval.
RA/CVD = rheumatoid arthritis/collagen vascular diseases; TCM = takotsubo cardiomyopathy; †HMO-Health Maintenance Organization.
* Cell column <11 were not reported as per HCUP privacy guidelines.

Table 2A
Outcomes of chemotherapy-related hospitalizations with versus without takotsubo cardiomyopathy: unmatched

Outcomes	Takotsubo cardiomyopathy		p value
	NO (n = 1,067,415)	YES (n = 562)	
All-cause in-hospital mortality	34,582 (3.2%)	103 (18.3%)	**< 0.001**
Disposition of patient			**< 0.001**
Routine	782,571 (73.3%)	212 (37.7%)	
Transfer to short-term hospital	6,998 (0.7%)	< 11*	
Other transfers (SNF, ICF, other)	75,408 (7.1%)	104 (18.6%)	
Home health care	164,820 (15.4%)	133 (23.6%)	
Length of stay median (Q1, Q3)	5 days (5, 6)	17 days (15, 19)	**< 0.001**
Total hospital charges median (Q1, Q3)	$46,335 ($46,201, $46,469)	$162,825 ($140,707, $222,073)	**< 0.001**

$p < 0.05$ (bold values) indicate clinical significance.
ICF = intermediate care facility; Q1 = first quartile; Q3 = third quartile; SNF = skilled nursing facility; TC = takotsubo cardiomyopathy.
* Cell values < 11 were not reported as per HCUP guidelines to publish using the NIS database.

Table 2B
Outcomes in chemotherapy-related hospitalizations with versus without takotsubo cardiomyopathy: a propensity-matched analysis

Outcomes	Takotsubo cardiomyopathy		p value
	NO (n = 498)	YES (n = 498)	
All-cause in-hospital mortality	< 11*	88 (17.7%)	**< 0.001**
Disposition of patient			**< 0.001**
Routine	442 (89.0%)	177 (35.5%)	
Transfer to short-term hospital	21 (4.2%)	< 11*	
Other transfers (SNF, ICF, other)	13 (2.6%)	99 (19.9%)	
Home health care	< 11*	124 (24.9%)	
Length of stay median (Q1, Q3)	1 day (1, 1)	17 days (15, 19)	**< 0.001**
Total hospital charges median (Q1, Q3)	$7,600 ($6,983, $9,362)	$162,825 ($140,707, $222,073)	**< 0.001**

$p < 0.05$ (bold values) indicate clinical significance.
ICF = intermediate care facility; Q1 = first quartile; Q3 = third quartile; SNF = skilled nursing facility; TC = takotsubo cardiomyopathy.
* Cell values < 11 were not reported as per HCUP guidelines to publish using the NIS database.

Table 3
Univariate predictors of in-hospital mortality in patients receiving chemotherapy with takotsubo cardiomyopathy

Predictors	Odds ratio	95% CI LL-UL*	p value
Age at hospitalization ≥85 years vs. 18-44 years	7.77	1.6-37.72	**0.011**
Male vs. Female	1.15	0.73-1.81	0.560
African American vs. white	0.28	0.10-0.73	**0.010**
Asian/Pacific Islander vs. white	8.21	2.70-24.96	**< 0.001**
Non-elective vs. Elective admission	1.36	0.86-2.16	0.185
Urban teaching vs. urban non-teaching hospital	2.86	1.07-7.64	**0.036**
Northeast vs. South region hospitals	2.70	1.35-5.43	**0.005**
Midwest vs. South region hospitals	3.83	1.97-7.43	**< 0.001**
West vs. South region hospitals	4.74	2.38-9.40	**< 0.001**
0-25th vs. 25-50th percentile household income	1.98	1.00-3.91	**0.049**
75-100th vs. 25-50th percentile household income	2.07	1.06-4.07	**0.034**
Private including HMO[†] vs. Medicare	2.80	1.74-4.51	**< 0.001**
Year 2011 vs. 2010	6.27	2.35-16.78	**< 0.001**
Year 2014 vs. 2010	2.85	1.05-7.75	**0.041**
Length of stay (days)	1.02	1.01-1.03	**< 0.001**
Septicemia	8.95	5.57-14.37	**< 0.001**
Fluid-electrolyte disorders	8.36	4.24-16.46	**< 0.001**
Cardiogenic shock	7.15	3.08-16.59	**< 0.001**
Respiratory failure	3.81	2.44-5.96	**< 0.001**

* CI = confidence interval; LL = lower limit; UL = upper limit; $p < 0.05$ indicates clinical significance.
[†] HMO = Health Maintenance Organization.

chemotherapy-related hospitalizations in cancer patients. To understand this burden, it is essential to appreciate the incidence of TC in this patient population. We identified a mean incidence rate of 53.0 new TC cases per 100,000 hospitalized chemotherapy patients with a significant growth rate of 8.6 new TC cases per 100,000 chemotherapy patients per year. The mean age of hospitalizations with TC was higher when compared with those without TC. With reference to gender predisposition, our study reported an approximate 7:3 female to male ratio, which is almost similar to the 9:1 ratio in overall TC cases in the Western countries.[16,17]

In terms of the baseline characteristics, the major differences observed in both groups were the higher mean age at admission, the predominance of patients >45 years of age, and a female gender predominance in the TC group. An earlier review identified a lower mean age of 53.6 years and a wider SD ±23.7. Coen et al conducted a systematic review of cases with chemotherapy-associated TC from the year 2000 onward and found 27 case reports, of whom 14 (52%) were men and 13 (48%) women with an overall younger (mean age 54 years vs our study 63 years) study cohort.[18] One possible explanation for this discrepancy could be due to nonreporting of the TC cases in the elderly populations as opposed to younger ones.

Whether the development of TC in patients receiving chemotherapy is related to the underlying malignancy, a direct side effect of chemotherapy, catecholamine surge from either a physical or emotional stressor or a combination of etiologies is difficult to ascertain. However, a high nonelective admission rate (72.1%) in the TC patients suggests that it could mainly be due to a direct side effect of chemotherapy. A number of chemotherapies and related oncologic agents have been reported as the suspected causes of TC with multiple theories for its development.[13,18−21]

The prevalence of co-morbidities was higher in patients with TC, which could be associated with older age. It has been shown that the development of TC is more common in patients with a history of cardiovascular disorders.[10] In our study, there were strikingly notable differences between the groups in terms of the incidence of congestive heart failure (CHF) and lymphoma. TC patients had a 3.4-fold higher prevalence of lymphoma than non-TC patients (12.3% vs 3.6%). CHF was coded as a secondary diagnosis in almost half of the TC patients (45.4%) compared with only 4.2% in those without TC. This suggests a probable correlation of cancer and chemotherapy to the ventricular dysfunction regardless of its previous existence. In previous studies, obesity has shown worse outcomes in patients with TC[22]; however, the frequency of obesity in TC patients was comparatively lower which could be due to the effects of chemotherapy and cancer.

We observed a significantly increased mortality rate in the TC group (18.3% vs 3.2%) when unmatched patients were compared. This significance persisted even after the propensity-score matching (17.7%). To explain the increased mortality in the TC group, we evaluated the predictors of in-hospital mortality. An advanced age, Asian race, urban teaching hospital admissions, and clinical complications including septicemia, fluid-electrolyte disorders, cardiogenic shock, and respiratory failure were found to be intimately predictive of in-hospital mortality.

Among chemotherapy-related hospitalizations, TC patients were more likely to require home healthcare or an advanced level care facility at the time of discharge. The propensity-matched analysis showcased striking differences between the LOS (median 17 vs 1 day) and total hospital charges (median $162,825 vs $7,600) which raises major concerns about increased healthcare burden. There were no other significant differences in both groups apart from elective vs nonelective admission rates, hospital and payer characteristics. This suggests that the difference in hospital charges were mainly due to the increased LOS in TC patients.

As with any administrative database study, this study has a few potential limitations. Under-reporting and over-reporting of TC could be a limitation. Due to the unavailability of the echocardiographic findings, and distinct codes for preexisting and new-onset ventricular dysfunction, it is possible that a few CHF cases represent previous CHF in addition to transient heart failure syndrome caused by chemotherapy-related heart failure (HF). By focusing on inpatient chemotherapy as the total population at risk for developing TC, we could not include patients that may have developed stress cardiomyopathy in an outpatient setting after having received chemotherapy. Although we excluded patients with a primary discharge diagnosis of the acute coronary syndrome from the final study cohort, large administrative databases such as NIS still carry possibilities of selection bias (e.g.. septic cardiomyopathy) to some extent because TC is a diagnosis of exclusion. Nonetheless, using the NIS, we could acquire meaningful results generalizable to a large US population.

We observed an overall increasing nationwide trend in TC incidence among adult patients receiving chemotherapy, which adds to significantly increased in-hospital mortality and healthcare finances. Many of the patients receiving inpatient chemotherapy could have been exposed to potentially cardiotoxic regimens and considering TC, in the setting of new-onset cardiomyopathy, as 1 of the sequels of chemotherapy allows for resourceful preventive strides to be investigated.

Disclosures

The authors have no conflicts of interest to disclose.

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