Article published online: 2022-07-14

Original Article

Predisposing Factors and Health-Care Utilization in Liver Transplant Recipients with Takotsubo Cardiomyopathy: A National Analysis

Kishan Patel[1], Salman K. Bhatti[2], Sylvester M. Black[3], Kyle Porter[4], James Hanje[1,5], Khalid Mumtaz[1,5]

[1]Department of Internal Medicine, Ohio State University Wexner Medical Center, [2]Division of Cardiovascular Medicine, Ohio State University Wexner Medical Center, [3]Department of Transplant Surgery, Ohio State University Wexner Medical Center, [4]Department of Biomedical Informatics, Center for Biostatistics, College of Medicine, Ohio State University, [5]Division of Gastroenterology, Hepatology, and Nutrition, Ohio State University Wexner Medical Center, Columbus, Ohio, USA

Abstract

Aims and Objectives: Takotsubo cardiomyopathy (TCMP) is an acquired cardiomyopathy associated with physical, emotional, and surgical stress. Current literature on TCMP in liver transplant recipients (LTRs) is limited to case reports and case series. **Methods:** The Nationwide Readmission Database was utilized to identify all adults with an index admission for LT between 2010 and 2014 who developed TCMP. The prevalence of TCMP at the LT admission or readmission within the calendar year was examined. Predictors of development and health-care utilization of patients with and without TCMP in LTR were compared. Multivariable regression analysis was performed. **Results:** The prevalence of TCMP in LTRs was found to be 0.5% (141/28,067). Most of these patients developed early TCMP on the index admission for LT ($n = 115$; 82%). Older (57.5 ± 1.3 vs. 55.1 ± 0.3 years, $P < 0.001$) females (adjusted odds ratio [aOR]: 2.27; confidence interval [CI]: 1.20–4.27; $P = 0.01$) with ≥4 Elixhauser comorbidity (aOR: 2.36; CI: 1.15–4.83; $P = 0.02$) were predisposed to develop TCMP in LTRs. LT at a medium-sized center (aOR: 0.17; CI: 0.03–0.88) has a protective effect on the development of TCMP. Increased health-care utilization in the form of mechanical ventilation, hemodialysis, vasopressors, and intra-aortic balloon pumps is observed in patients with TCMP. This resulted in increased length of stay and cost in patients with TCMP. Moreover, increased mortality was seen in patients who developed TCMP within the same calendar year. **Conclusion:** This is the first report showing the prevalence of TCMP in LTRs to be 0.5%. Older females with increased comorbidity are predisposed to TCMP. Patients who developed TCMP necessitate a higher acuity of medical care and cause an increased health-care burden and ultimately experience an increase in mortality.

Keywords: Database, female, liver transplantation, outcomes, Takotsubo cardiomyopathy

Address for correspondence: Dr. Khalid Mumtaz, 395 W. 12th Avenue, 2nd Floor, Division of Gastroenterology, Hepatology and Nutrition, Columbus, Ohio, USA. E-mail: khalid.mumtaz@osumc.edu

Submitted: 21-Oct-2020 **Revised:** 15-Nov-2020
Accepted: 22-Nov-220 **Published:** 04-Nov-2020

How to cite this article: Patel K, Bhatti SK, Black SM, Porter K, Hanje J, Mumtaz K. Predisposing factors and health-care utilization in liver transplant recipients with Takotsubo cardiomyopathy: A national analysis. Ibnosina J Med Biomed Sci 2020;12:300-6.

Access this article online

Quick Response Code:

Website: www.ijmbs.org

DOI: 10.4103/ijmbs.ijmbs_131_20

Introduction

Takotsubo cardiomyopathy (TCMP) is an acquired cardiomyopathy with transient systolic and diastolic dysfunction characterized by apical left ventricular dysfunction or other noncoronary distribution wall motion abnormalities. It is classically associated with physical and emotional stress. However, it is now recognized that TCMP can also occur in the setting of acute medical illness and after surgery.[1,2] Transthoracic echocardiography typically demonstrates left ventricular apical ballooning with basal hyperkinesis and is associated with new electrocardiographic abnormalities such as transient ST-segment elevation with a notable absence of obstructive coronary disease on cardiac catheterization.[3] TCMP has been rarely reported in liver transplantation recipients (LTRs), with only few cases reported in the literature.[4-7] Approximately 20 cases of TCMP were recorded in the LT registry of Toronto General Hospital, Ontario, Canada, from approximately 1000 LTs performed in the last 10 years (personal communication). This gives a prevalence of TCMP of approximately 2% in LTRs from a single center.

Severe cases of TCMP may require vasopressor or inotropic therapy, oxygenation and mechanical ventilation, or the placement of an intra-aortic balloon pump or extracorporeal membrane oxygenation,[1,3,8] resulting in a significant burden on health-care utilization. Due to rarity of this condition and reported cases, no specific intra-LT or post-LT predictors have been reported to increase the risk for TCMP.[9] Epidemiology, predictors, and outcomes in LTRs who subsequently develop TCMP are lacking. However, the use of extensive health-care resources due to TCMP in an already tenuous LTR demand further study of trends, prevalence, predictors, and clinical outcomes.

Methods

The Nationwide Readmissions Database (NRD) 2010–2014 was queried using specific International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. The NRD, drawn from the Health-care Cost and Utilization Project, consists of 21 State Inpatient Databases containing patient linkage numbers that can be used to track patients through multiple admissions. The database also contains information on patient demographics, hospital characteristics, procedures performed, and discharge diagnoses that can be extrapolated to provide national estimates.

TCMP was identified by the ICD-9 code 429.83[10,11] while LTRs were identified using ICD-9-CM procedural codes for LT. Codes for a history of LT were avoided intentionally to ensure capture of TCMP after LT. Decompensated cirrhosis was defined by the presence of an ICD-9-CM code for cirrhosis in addition to an ICD-9-CM code for either ascites, encephalopathy, esophageal bleeding, or spontaneous bacterial peritonitis [Supplementary Table 1]. As we aimed to measure TCMP development after LT, "cases" were regarded as patients with index admissions with a procedural code for LT who developed TCMP, whereas "controls" were patients who underwent LT without developing TCMP through either the index admission or the calendar year. Patients with multiple organs transplantation (e.g., liver with lung, heart, pancreas, or kidney) and pregnant females were excluded. Early TCMP was defined as the development of TCMP during the index admission of LT while late TCMP was defined as TCMP after the initial hospitalization. Outcomes examined were mortality and hospital resource utilization, including length of stay (LOS) and hospital costs. Predictors of TCMP development within the LTRs were analyzed.

Statistical analysis

All statistical analyses accounted for the NRD weights and stratified sampling design (discharge weights, stratification, and clustering). Univariate comparisons of patient characteristics between patients with and without TCMP were made by the Chi-square test for categorical variables and linear regression for continuous variables. A weighted logistic regression model was used to identify the variables associated with developing TCMP at index admission or readmission. All variables from Table 1 with a $P < 0.05$ were included in the multivariate model. The presence of specific agency for Healthcare Research and Quality Comorbidities were compared by the Chi-square test. Linear

Table 1: Demographics, hospital characteristics, and interventions in Takotsubo cardiomyopathy in liver transplant recipients

Variable	With Takotsubo cardiomyopathy[a] (*n*=141; 0.5%), *n* (%)	Without Takotsubo cardiomyopathy[a] (*n*=27,926; 99.5%), *n* (%)	*P*
Age, mean±SE	57.5±1.3	55.1±0.2	<0.001
Sex			
Male	66 (46.7)	18,614 (66.7)	0.004
Female	75 (53.3)	9311 (33.3)	
Elixhauser comorbidities			
<4	14 (9.8)	10,385 (37.2)	<0.001
≥4	127 (90.2)	17,540 (62.8)	
Hospital bed size			<0.001
Small	28 (19.7)	1872 (6.7)	
Medium	<10 (1.1)	2175 (7.8)	
Large	111 (79.1)	23,879 (85.5)	
Length of stay and 10-day threshold			<0.001
<10 days	<10 (6.1)	12,970 (46.4)	
≥10 days	132 (93.9)	14,956 (53.6)	
Length of stay and median (IQR)	26.6 (20.4-43.3)	10.8 (6.9-23.1)	<0.001
Hospital cost index admission, median (IQR)	148,274 (110,983-226,570)	89,879 (65,858-136,135)	<0.001
Calendar year readmission costs, median (IQR)[b]	35,886 (11,801-64,002)	18,428 (7,781-45,472)	<0.001
Cirrhosis etiology			0.18
Alcoholic	50 (35.3)	7159 (25.6)	
Nonalcoholic	66 (47.2)	13,504 (48.4)	
No cirrhosis coded	25 (17.6)	7263 (26.0)	
Decompensated cirrhosis	108 (77.1)	14,760 (52.9)	<0.001
Ascites	103 (73.4)	13,494 (48.3)	<0.001
Encephalopathy	76 (54.4)	7600 (27.2)	<0.001
Variceal bleeding	<10 (1.4)	111 (0.4)	0.20
Spontaneous bacterial peritonitis	<10 (1.6)	1331 (4.8)	0.25
Portal hypertension	94 (66.8)	10,973 (39.3)	<0.001
In-hospital procedures			
Mechanical ventilation	89 (63.1)	9428 (33.8)	<0.001
Hemodialysis	107 (76.2)	13,291 (47.6)	<0.001
Infusion of intravenous vasopressor	26 (18.8)	1095 (3.9)	<0.001
Intra-aortic balloon pump	<10 (5.2)	34 (0.1)	<0.001
In-hospital outcomes			
Early TCMP[c]	115 (82.1)	N/A	N/A
Late TCMP[d]	38 (27.1)	N/A	N/A
Mortality at index	<10 (7.0)	1105 (4.0)	0.20
Mortality at readmission within calendar year	<10 (5.4)	484 (1.7)	0.02

[a]At index or readmission within the calendar year, [b]Included only patients with at least 1 readmission, [c]During index admission for transplant, dAfter index admission for liver transplant. SE: Standard error, IQR: Interquartile range, TCMP: Takotsubo cardiomyopathy, N/A: Not available

temporal trends were tested by linear regression on the yearly frequency estimates weighted by the inverse variance of those estimates. A significance level of $\alpha = 0.05$ was used for all analyses. All analyses were performed using the SAS version 9.4 (Cary, NC) by a biostatistician.

Results

Trends of Takotsubo cardiomyopathy

A total of 28,067 patients underwent LT between the years 2010 and 2014. Of these, TCMP occurred in 0.5% (141/28,067) of all LTRs. Early TCMP developed in 115 (82.1%) while late TCMP in 38 (17.9%.) LTRs. The trends of both LTs and cases of TCMP annually between 2010 and 2014 remained stable [Supplementary Table 2].

Univariate analysis

Patients with TCMP [Table 1] were more likely to be older (57.5 ± 1.3 vs. 55.1 ± 0.2 years, $P < 0.001$), females (53.3% vs. 33.3%, $P = 0.004$), with 4 or more Elixhauser comorbidities (90.2 vs. 62.8%, $P < 0.001$)

as compared to LTRs without TCMP. Other predictors of TCMP development included decompensated cirrhosis (77.1% vs. 52.9%, $P < 0.001$) with ascites (73.4% vs. 48.3%, $P < 0.001$), hepatic encephalopathy (54.4% vs. 27.2%, $P < 0.001$), and portal hypertension (66.8% vs. 39.3%, $P < 0.001$). TCMP developed more frequently in LTRs in smaller bed size hospitals (19.7% vs. 6.7%, $P < 0.001$).

After LT, TCMP patients required higher resource utilization in the form of mechanical ventilation, hemodialysis, vasopressors, and intra-aortic balloon pumps (IABP). TCMP patients not only experienced a longer LOS (median: 26.6; interquartile range [IQR]: 20.4–43.3 vs. median: 10.8 days; IQR: 6.9–23.1, $P < 0.001$) but also incurred a higher cost on index hospital admission (median: $148,274; IQR: 110,983–226,570 vs. $89,879; IQR: 65,858–136,135; $P < 0.001$). Moreover, in patients who were readmitted at least once, TCMP patients had significantly higher readmission costs ($35,886; IQR: 11,801–64,002 vs. $18,428; IQR: 7,781–45,472, $P < 0.001$).

Although index admission mortality did not differ significantly between cases and controls (7.0% vs. 4.0%, $P = 0.20$), mortality during readmissions within the calendar year was higher in LTRs with TCMP (5.4% vs. 1.7%, $P = 0.02$). Specific comorbidities that were commonly seen in TCMP patients are shown in Table 2.

Multivariate analysis

Female gender (adjusted odds ratio [aOR]: 2.27; confidence interval [CI]: 1.2–4.27) and 4 or more Elixhauser comorbidities (aOR: 2.36; CI: 1.15–4.83) were the independent predictors of development of TCMP in LTRs [Table 3]. LT at a medium sized hospital was associated with lower odds of developing TCMP (aOR: 0.17; CI: 0.03–0.88). Decompensated cirrhosis (aOR: 1.58; CI: 0.93–2.67), presence of portal hypertension (aOR: 1.70; CI: 0.97–2.97), receiving mechanical ventilation (aOR: 1.96; CI: 0.90–4.26), and hemodialysis (aOR: 1.98; CI: 0.94–4.15) were found to be marginally associated with the development of TCMP. Patients with TCMP utilized increased hospital resources in the form of vasopressors (aOR: 3.62; CI: 2.01–6.51) and IABP (OR: 83.3; CI: 25.2–274.8) after LT as compared to those without it.

Discussion

Takosubo cardiomyopathy has been reported to be associated to with significant morbidity and mortality in the general population. The American Heart Association incorporated it under the class of acquired cardiomyopathies in 2006.[12] To date, no statistical analysis on its prevalence, predisposing factors, hospital resource utilization, and mortality is available in LTRs. Therefore, we analyzed TCMP in LTRs using a large national database. The prevalence of TCMP in LT was found to be 0.5%, with the majority of cases occurring early during the index admission for LT. Older females with ≥4 Elixhauser comorbidity index were at increased risk of developing TCMP after LT. Increased resource utilization, in the form of invasive interventions such as vasopressors and IABP, was observed in

Table 2: Significant elixhauser comorbidity variables comparing liver transplant recipients with and without takotsubo cardiomyopathy

Variable	LT with Takotsubo cardiomyopathy[a] (*n*=141; 0.5%), *n* (%)	LT without Takotsubo cardiomyopathy[a] (*n*=27,926; 99.5%), *n* (%)	*P*
Deficiency anemias	56 (39.7)	6835 (24.5)	0.02
Rheumatoid arthritis	<10 (2.1)	355 (1.3)	0.01
Chronic blood loss anemia	12 (8.8)	495 (1.8)	0.03
Congestive heart failure	59 (41.6)	890 (3.2)	<0.001
Coagulopathy	103 (73.5)	1,738 (52.8)	0.001
Fluid and electrolyte disorders	126 (89.8)	15,274 (54.7)	<0.001
Renal failure	39 (27.4)	4160 (14.9)	0.02
Solid tumor without metastasis	16 (11.2)	6358 (22.8)	0.02
Valvular disease	14 (9.8)	895 (3.2)	<0.001
Weight loss	69 (49.1)	6995 (25.0)	<0.001

[a]At index or within calendar year readmission. LT: Liver transplant

Table 3: Multivariable logistic regression analysis[a] of predictors and resource utilization in Takotsubo cardiomyopathy[b]

Variable	Adjusted OR (95% CI)	Multivariable *P*
Female sex	2.27 (1.20-4.27)	0.01
Elixhauser index ≥4	2.36 (1.15-4.83)	0.02
Hospital bed size		
Small	1.91 (0.99-3.70)	0.06
Medium	0.17 (0.03-0.88)	0.04
Large	Reference	
Decompensated cirrhosis	1.58 (0.93-2.67)	0.09
Portal hypertension	1.70 (0.97-2.97)	0.06
Mechanical ventilation	1.96 (0.90-4.26)	0.09
Hemodialysis[c]	1.98 (0.94-4.15)	0.07
Infusion of intravenous vasopressor[c]	3.62 (2.01-6.51)	<0.001
Intra-aortic balloon pump[c]	83.3 (25.2-274.8)	<0.001

[a]All patients or hospital characteristics with $P \leq 0.05$ from Table 1 were included in the multivariable model. There were not enough TCMP events to support a model which included all variables from table, [b]At index or readmission within the calendar year, [c]Measures of resource utilization. OR: Odds ratio, CI: Confidence interval, TCMP: Takotsubo cardiomyopathy

patients with TCMP. We also demonstrated that TCMP patients have increased LOS and cost of index admission for LT and ultimately suffer higher calendar year mortality.

Previous reports using a national inpatient sample database showed that TCMP was diagnosed in about 0.02% of all hospitalizations in the United States.[13] Comparatively, the prevalence of TCMP in LTRs is nearly 25 times higher in our study. As TCMP is thought to be related to stress and precipitated in part or entirely by excessive catecholamine stimulation of the myocardium,[1,2] increased occurrence could be due to the extreme physical stress and subsequent catecholamine release as a result of LT. This is endorsed by our personal communication from a single transplant center in Canada where they found TCMP in approximately 2% of their LTRs. The trend of TCMP is thought to be increasing, although likely due to increased recognition of this disease entity and increased severity of liver disease in LTRs rather than true increased incidence.[14,15]

Conforming to the typical scenario of TCMP, females with LT were more likely to develop TCMP than their male counterparts. Whereas previous studies showed women accounting for upward of 90% of all TCMP cases, we found that only 53% of TCMP were females.[14,15] However, female gender more than doubled the odds of TCMP with LT. The cause of apparent female predisposition for TCMP is unknown but could be related to gender differences in myocardial sensitivity to catecholamine toxicity,[16] which may make less of a difference in the setting of a significant stress event such as LT.

We found an increased (≥4) number of Elixhauser comorbidity to increase the odds of the development of TCMP. In studies on the general population, obesity, hypertension, uncomplicated diabetes, and pulmonary disease were reported to be associated with TCMP.[17] In our study, the presence of congestive heart failure, coagulopathy, electrolyte imbalances, and valvular disease were increasingly associated with TCMP development. Common comorbidity in our and previously reported studies on TCMP was chronic renal disease and malignancy.[17-19]

TCMP drastically increases the resource utilization during hospitalization. In 2014, the total average cost of a LT was approximately $739,100,[20] posing an already significant burden on the health-care system. We found the median cost of LTRs with TCMP almost doubled when compared to LTRs without TCMP. While evidence is lacking in the TCMP setting, a previous European study found the cost of IABP support in acute myocardial infarction to be more than medical therapy alone.[21] LOS has been used as a valid surrogate for hospital costs.[22] The median LOS for TCMP patients was more than double that of non-TCMP patients. Moreover, more than one-fourth of our patients developed TCMP on a nonindex admission, with the added cost of readmissions to be upward of $40,000 on average which represents a significant health care resource expenditure.[23]

Cardiovascular disease is a common cause of mortality and morbidity after LT.[24] Inpatient mortality from all cardiovascular events following LT has been previously found to be 4%.[25] Comparatively, our results show LTRs with TCMP suffered from an increased calendar year mortality

rate as compared to patients without TCMP. Moreover, TCMP in the overall population had a mortality rate of 2%–4%.[10,26] In contrast, we found the occurrence of TCMP had 5.4% mortality in the post-LT setting.

Our study has multiple limitations inherent to administrative database analysis research. First, this study relies on ICD9-CM codes for establishing diagnoses. Theoretically, under/miscoding can lead to misclassification bias. However, NRD has been used to study readmission in several medical and surgical conditions.[27,28] It is possible that that few cases of cirrhotic cardiomyopathy were not diagnosed before the LT and resulted in decompensated heart failure in the postoperative time period. However, TCMP is a distinct entity from cirrhotic cardiomyopathy with characteristic wall motion pattern and is unlikely to be confused with cirrhotic cardiomyopathy. Furthermore, cirrhotic cardiomyopathy tends to get better after LT. Due to the high positive predictive value of the TCMP ICD-9-CM code used in a European study,[29] we tend to believe that most cases captured in our study represent true TCMP cases. The Mayo diagnostic criteria and diagnostic criteria by Kawai *et al*. for TCMP require coronary angiography to exclude coronary artery obstruction.[2,30] Furthermore, LTRs undergo a substantial cardiac work up, including electrocardiogram, echocardiogram, and coronary angiography before LT, with abnormal findings precluding patients to transplant. The NRD is limited to specific data and notably lacks laboratory values, specific imaging and procedure results, and medication usage. We were unable to present the Model for End-Stage Liver Disease score which inform us about the severity of cirrhosis. However, we used codes for decompensated cirrhosis reported in previous publications.[31] Furthermore, data extraction from the NRD relies on the use of ICD-9-CM codes, which can vary in quality of diagnosis coding or documentation. Nevertheless, the large sample size provided by the NRD increases statistical power to analyze this uncommon condition.

Conclusion

In conclusion, this is the first study from the US reporting prevalence and trends of TCMP and its risk factors in the post-LT population. Predisposing factors leading to the development of TCMP in post-LT patients include older age, female gender, decompensated cirrhosis, and a higher number of comorbidities. With the number of LTs increasing[32] along with increasing selection of more critical patients, the number of TCMP cases in LTRs is likely to increase, calling for further research into early identification of TCMP and improving clinical outcomes in this rarely reported post-LT complication. The presence of TCMP was associated with increased health-care utilization and cost which translated into a possibly increased mortality. Further research should elucidate optimal prevention strategy and management of TCMP in post-LT recipients.

Author's contributions

All authors have approved the final version of the manuscript.

Kishan Patel: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content.

Salman Bhatti: critical revision of the manuscript for important intellectual content.

Sylvester Black: critical revision of the manuscript for important intellectual content.

Kyle Porter: acquisition of data, analysis and interpretation of data, statistical analysis, critical revision of the manuscript for important intellectual content.

James Hanje: critical revision of the manuscript for important intellectual content.

Khalid Mumtaz: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Reviewers:	Editors:
Hussien Elsiesy (Tucson, AZ, USA)	Elmahdi A Elkhammas (Columbus OH, USA)

Supplementary Table 1: International Classification of Diseases, Ninth Revision, Clinical modification codes used for data extraction and analysis from the Nationwide Readmission Database 2013

	ICD-9-CM codes used	Variable location
Diagnosis		
Takotsubo's cardiomyopathy	429.83	DX1
Cirrhosis - nonalcoholic	571.5, 571.6	DX2-DX25
Cirrhosis - Alcoholic	571.2	DX2-DX25
Decompensated	Any cirrhosis code (571.2, 571.5, 571.6) and at least one of the below	DX2-DX25
Ascites	789.5, 789.59	
Encephalopathy	348.30, 348.39, 572.2, and 780.97	
Variceal bleeding	456.0	
Spontaneous bacterial peritonitis	567.23	
Acute respiratory failure and mechanical ventilation	518.0, 518.81, 518.82, 518.84	DX2-DX25
Acute kidney injury and hemodialysis	584.5, 584.6, 584.7, 584.8, 584.9, 586	DX2-DX25
Intra-abdominal infections	567.2, 567.1, 567.29, 567.22, 567.38, 567.39	DX2-DX25
Sepsis and septic shock	785.52, 038, 995.9	DX2-DX25
Postoperative shock	998.0	DX2-DX25
Procedural codes		
Liver transplantation	50.5, 50.51, 50.59	PR1
Acute respiratory failure and mechanical ventilation	93.90, 96.01, 96.02, 96.03, 96.04, 96.05, 96.70, 96.71, 96.72	PR2 to PR15
Infusion of intravenous vasopressor	00.17	PR2 to PR15
Intra-aortic balloon pump	37.61	PR2 to PR15
ECMO	39.65, 39.66	PR2 to PR15
Acute kidney injury and hemodialysis	39.95	PR2 to PR15
Postsurgery laparotomy	39.98, 54.12	PR2 to PR15
Blood transfusion	99.00, 99.02, 99.03, 99.04, 99.05, 99.05, 99.07	PR2 to PR15
Transplantation codes		
Kidney transplantation	V42.0, 55.6, 55.61, 55.69	DX2-DX25
Heart transplantation	V42.1, 33.6, 37.51	DX2-DX25
Lung transplantation	V42.6, 33.5, 33.50, 33.51, 33.52	DX2-DX25
Pancreas transplantation	V42.83, 52.8, 52.80, 52.81, 52.82, 52.83, 52.84, 52.85, 52.86	DX2-DX25
Intestinal transplantation	V42.84, 46.97	DX2-DX25

AHRQ: Agency of Health-care Research and Quality, ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification, ECMO: Extracorporeal membrane oxygenation

Supplementary Table 2: Temporal trends of Takotsubo cardiomyopathy in liver transplant recipients between 2010 and 2014, Nationwide Readmission Database

Variable	2010	2011	2012	2013	2014	*P* for linear trend[a]
Liver transplants[b]	5586	5800	5604	5490	5587	0.44
TCMP	18	≤10	29	45	39	0.08
Decompensated cirrhosis	2715	3001	2806	2979	3367	0.10
Age ≥50	4243	4517	4438	4289	4392	0.91
Female	1954	1859	1779	1927	1867	0.89

[a]Patients with liver transplant procedures meeting inclusion criteria, [b]Tested by linear regression on the yearly frequency estimates weighed by the inverse variance. TCMP: Takotsubo cardiomyopathy