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WJH mainly publishes articles reporting research results and findings obtained in the field of hepatology and covering a wide range of topics including chronic cholestatic liver diseases, cirrhosis and its complications, clinical alcoholic liver disease, drug induced liver disease autoimmune, fatty liver disease, genetic and pediatric liver diseases, hepatocellular carcinoma, hepatic stellate cells and fibrosis, liver immunology, liver regeneration, hepatic surgery, liver transplantation, biliary tract pathophysiology, non-invasive markers of liver fibrosis, viral hepatitis.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Takotsubo cardiomyopathy in orthotopic liver transplant recipients: A cohort study using multi-center pooled electronic health record data

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Abstract

BACKGROUND

Takotsubo cardiomyopathy (TCM), or stress-induced cardiomyopathy, is associated with adverse prognosis. Limited data suggest that TCM occurring in orthotopic liver transplant (OLT) recipients is associated with elevated peri-operative risk.

AIM

To characterize the predictors of TCM in OLT recipients, using a large, multi-center pooled electronic health database.

METHODS

A multi-institutional database (Explorys Inc, Cleveland, OH, USA), an aggregate of de-identified electronic health record data from 26 United States healthcare systems was surveyed. A cohort of patients with a Systematized Nomenclature of Medicine-Clinical Terms of "liver transplant" between 09/2015 and 09/2020 was identified. Subsequently, individuals who developed a new diagnosis of TCM following OLT were identified. Furthermore, the risk associations with TCM among this patient population were characterized using linear regression.

RESULTS

Between 09/2015 and 09/2020, of 37718540 patients in the database, 38740 (0.10%) had a history of OLT (60.6% had an age between 18-65 years, 58.1% female). A new diagnosis of TCM was identified in 0.3% of OLT recipients (45.5% had an age between 18-65 years, 72.7% female), compared to 0.04% in non-OLT patients [odds ratio (OR): 7.98, 95% confidence intervals: 6.62-9.63, (P < 0.0001)]. OLT recipients who developed TCM, compared to those who did not, were more likely to be greater than 65 years of age, Caucasian, and female (P < 0.05). There was also a significant association with cardiac arrhythmias, especially ventricular arrhythmias (P < 0.0001).

CONCLUSION

TCM was significantly more likely to occur in LT recipients *vs* non-recipients. Older age, Caucasian ethnicity, female gender, and presence of arrhythmias were significantly associated with TCM in LT recipients.

Key Words: Takotsubo cardiomyopathy; Orthotopic liver transplant; Stress-induced cardiomyopathy; Clinical outcomes

Core Tip: In a large cohort study using de-identified pooled electronic health record data, liver transplant recipients were more likely to develop Takotsubo cardiomyopathy compared to non-recipients. Older age, Caucasian ethnicity, female gender, and presence of arrhythmias were significantly associated with Takotsubo cardiomyopathy in liver transplant recipients.

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INTRODUCTION

Takotsubo cardiomyopathy (TCM) is a stress-induced, reversible cardiomyopathy that occurs in the absence of significant coronary artery disease[1]. The awareness of TCM, which was first reported in Japan in 1990, has increased rapidly and several nomenclatures for this condition have been proposed including stress-induced cardiomyopathy, apical ballooning syndrome, left ventricular ballooning, and broken heart syndrome[2,3]. TCM is believed to be related to the presence of an underlying pathological stress, whether physical or emotional[1]. Despite the enormous attention that this condition has gained in recent years, TCM is still considered to be underdiagnosed, with an underestimated risk and incompletely understood pathogenesis[4].

It is hypothesized that emotional or physical stress may trigger a surge in catecholamine secretion, which in turn can lead to microvascular spasms and myocardial stunning *via* interaction with beta-adrenergic receptors, resulting in left ventricular systolic dysfunction[5]. Patients undergoing major surgery often have increased concentrations of catecholamines, caused by the physical and emotional stress of the perioperative period, which can contribute to the development of TCM[6]. Although TCM is self-limited and resolves completely without an adverse event in the majority of affected patients, it may result in significant morbidity and mortality in critically ill patients, such as liver transplant recipients, with estimated mortality rate of 10%-27%[7].

Small observational studies and case series have reported the occurrence of TCM in liver transplant recipients, but large cohort studies evaluating this association are lacking in the literature[6]. In addition to the stress imposed by the perioperative period, liver transplant candidates are particularly vulnerable to developing TCM due to the impaired stress response in the inflammatory milieu of hepatic cirrhosis

[8,9]. Therefore, we aimed to study TCM in liver transplant recipients, providing information about the demographic characteristics of these patients, and delineating this unique patient population's risk factors for TCM.

MATERIALS AND METHODS

Database

We conducted a retrospective, cohort study using a multicenter analytics and research platform developed by IBM Watson Health (Explorys Inc, Cleveland, OH, USA)[10]. At present, Explorys captures more than 70 million unique patients across all 50 states, and thus provides a broad regional and climatic distribution of source population. Diagnoses, findings, and procedures are arranged into the Systematized Nomenclature of Medicine - Clinical Terms (SNOMED-CT) hierarchy while prescription drug orders are mapped into SNOMED and RxNorm[11,12]. Patients with all types of insurance as well as those who self-pay are represented. Ethical review and informed consent were waived, since there are no identifiers associated with any of the patient data. The Explorys rounds cell counts to the nearest 10 and treats all cell counts between zero and 10 as equivalent in order to protect the identities of patients. The Explorys database has been used in multiple publications in gastroenterology, cardiology, oncology, neurology, and surgery[13,14].

Patient selection

Using the Explorys search tool, we identified all active patients in Explorys between 09/2015 and 09/2020 and selected those who underwent liver transplantation. Subsequently, a cohort of patients with a SNOMET-CT diagnosis of "takotsubo cardiomyopathy" was identified. Cases were compared to those who underwent liver transplantation without a history of TCM. Using SNOMED-CT codes, we identified possible associated medical conditions as well as disease outcomes.

Statistical analysis

Demographics and associated diseases were characterized by descriptive statistics. The overall period prevalence was calculated by dividing the total number of individuals with TCM by the total number of individuals in Explorys who underwent liver transplantation (2015-2020). The odds ratio (OR) for univariate analysis, its standard error and 95% confidence intervals (CI) were calculated according to Altman, 1991, using the MedCalc Statistical Software for Windows, version 19.4 (MedCalc Software, Ostend, Belgium) with a case-control design[15]. For all analyses, a 2-sided P value of <0.05 was considered statistically significant.

RESULTS

There were a total of 37718540 individuals in the database (2015-2020) with 38,740 (0.1%) who underwent liver transplantation. Baseline characteristics of patients with liver transplant and control groups are demonstrated in Table 1. The majority of patient who underwent OLT were adults (18-65 years old), female (58.1%), and Caucasian (77.8%). Among those who underwent liver transplantation, there were 110 patients with a diagnosis of TCM with a period prevalence rate of 0.3%. Rates of TCM among OLT patients and timing of diagnosis are shown in Figures 1 and 2, respectively.

Interval epidemiology and underlying associations of Takotsubo cardiomyopathy in OLT.

Of the 110 patients with the diagnosis of TCM, the majority were elderly (> 65 years old) (54.5%), female (72.7%), and Caucasian (90.9%) (Table 2). Patients with a diagnosis of TCM were more likely to have other medical diseases including hypertension (OR: 1.82, 95%CIs: 1.23-2.68, $P = 0.0027$), hyperlipidemia (OR: 1.68, 95%CIs: 1.14-2.48, $P = 0.009$), atherosclerosis (OR: 2.35, 95%CIs: 1.54-3.58, $P = 0.0001$), coronary artery disease (OR: 2.15, 95%CIs: 1.45-3.18, $P = 0.0001$), chronic kidney disease (OR: 2.27, 95%CIs: 1.56-3.31, $P < 0.0001$), sepsis (OR: 5.90, 95%CIs: 4.05-8.60, $P < 0.0001$), anxiety (OR: 2.76, 95%CIs: 1.90-4.02, $P < 0.0001$), and mood disorders (OR: 2.00, 95%CIs: 1.38-2.92, $P = 0.0003$) (Figure 3).

Outcomes of Takotsubo cardiomyopathy among patients with OLT.

Among patients with a history of OLT, patients who were diagnosed with TCM were more likely to have cardiogenic shock (OR: 12.61, 95%CIs: 6.52-24.4, $P < 0.0001$), and to require mechanical circulatory support with an intra-aortic balloon bump (OR: 19.22, 95%CIs: 7.66-48.21, $P < 0.0001$). These patients were also at a higher risk of developing cardiac arrest (OR: 9.52, 95%CIs: 5.84-15.52, $P < 0.0001$). Other complications include cerebrovascular accidents, liver failure, gastrointestinal bleeding, and an increased requirement of invasive mechanical ventilation and renal replacement therapy (Figure 4).

Table 1 Baseline characteristics of patients with liver transplant versus those without liver transplant (control group)

	Liver transplant		No liver transplant	
	n = 38740	%	*n* = 37679800	%
Takotsubo cardiomyopathy	110	0.3	13430	0.0
Age > 65	14780	38.2	8349380	22.2
Age 18-65	23470	60.6	22449470	59.6
Age < 18	500	1.3	6659540	17.7
Male	16230	41.9	16676780	44.3
Female	22510	58.1	20665100	54.8
Caucasian	30150	77.8	22446830	59.6
African American	6060	15.6	4315410	11.5
Obesity	840	2.2	5018440	13.3
Cardiomyopathy	1770	4.6	762420	2.0
Hypertension	390	1.0	3465120	9.2
Diabetes Mellitus	710	1.8	5484800	14.6
Hyperlipidemia	1220	3.1	10758820	28.6
Atherosclerosis	770	2.0	3848890	10.2
Coronary artery disease	730	1.9	3395870	9.0
Myocardial infarction	430	1.1	1528310	4.1
Ischemic heart disease	620	1.6	2285770	6.1
Chronic kidney disease	530	1.4	2052700	5.4
Alcohol abuse	80	0.2	1013590	2.7
Smoking	290	0.7	6369120	16.9
Sepsis	690	1.8	2101780	5.6
Atrial fibrillation	1030	2.7	2659760	7.1
Supraventricular arrhythmia	200	0.5	75580	0.2
Ventricular arrhythmia	590	1.5	415060	1.1

DISCUSSION

The diagnosis of end-stage liver disease (ESLD) carries a poor prognosis and is associated with increased cardiovascular risk[16]. It is well-known that orthotopic liver transplantation (OLT) is the treatment of choice for patients with irreversible ESLD due to the improved survival after transplantation[17]. Nowadays, with the high prevalence of ESLD, increasing numbers of patients are being referred for OLT[18,19]. Although OLT improves the survival of ESLD patients, post-operative complications that affect the outcomes and survival of this patient group may occur, including cardiac complications, such as TCM[6,20]. As such, it is imperative to perform careful preoperative cardiac risk evaluation prior to the transplantation[21].

The current study is the first national database study to assess the association between liver transplantation and the development of TCM. There are several important findings in this retrospective observational study. We found that liver transplant recipients were more likely to develop TCM compared to non-recipients. It is conceivable that OLT predisposes to TCM from a pathophysiologic standpoint, given the increased levels of stress, and thus, a higher catecholamine surge around the time of liver transplant surgery.

On further analysis of OLT subgroup based on occurrence of TCM, we found that the group of patients who developed TCM were more likely to be female, Caucasian, and elderly. This is consistent with prior epidemiological and clinical studies[22-24]. In a retrospective observational study that looked at various co-morbidities, it was found that patients with certain co-morbid conditions were more likely to have concurrent TCM, compared with age-matched control groups[25]. In that study, it was reported that sepsis, cerebrovascular accident, malignancy, and anxiety disorder increased the risk of TCM with an OR 13.94 (95%CI: 11.69-16.62), 10.81 (95%CI: 8.70-13.43), 1.73 (95%CI: 1.63-1.83), and 2.54 (95%CI:

Table 2 Baseline characteristics of patients with Takotsubo cardiomyopathy following liver transplant versus those without a history of Takotsubo cardiomyopathy following liver transplant (control group)

	Takotsubo cardiomyopathy		No takotsubo cardiomyopathy		*P* value
	n = 110	%	*n* = 38640	%	
Age > 65	60	54.5	14720	38.1	0.0005
Age 18-65	50	45.5	23400	60.6	0.0014
Age < 18	0	0.0	500	1.3	
Male	30	27.3	16200	41.9	0.0022
Female	80	72.7	22440	58.1	0.0022
Caucasian	100	90.9	30060	77.8	0.0016
African American	5	4.5	6060	15.7	0.0042
Obesity	30	27.3	10500	27.2	0.9814
Hypertension	40	36.4	9250	23.9	0.0027
Diabetes mellitus	60	54.5	17910	46.4	0.0867
Hyperlipidemia	70	63.6	19720	51.0	0.009
Atherosclerosis	30	27.3	5320	13.8	0.0001
Coronary artery disease	50	45.5	12280	31.8	0.0001
Chronic kidney disease	60	54.5	13350	34.5	< 0.0001
Alcohol abuse	10	9.1	3060	7.9	0.6499
Smoking	40	36.4	10930	28.3	0.0621
Sepsis	60	54.5	6530	16.9	< 0.0001
Atrial fibrillation	50	45.5	5470	14.2	< 0.0001
Supraventricular arrhythmia	60	54.5	6740	17.4	< 0.0001
Ventricular arrhythmia	5	4.5	210	0.5	< 0.0001
Anxiety disorder	60	54.5	11700	30.3	< 0.0001
Mood disorder	60	54.5	14470	37.4	0.0003
Seizure disorder	10	9.1	1750	4.5	0.025

2.34-2.75), respectively. Patients who developed TCM in our study were also more likely to have chronic medical conditions, which may have possibly predisposed them to this condition *via* coronary microcirculatory dysfunction, one of the mechanisms that was proposed as a contributor in the pathogenesis of TCM[26]. Importantly, patients who developed TCM were found to have higher rates of arrhythmias, including those of atrial and ventricular origin, which is an important finding, and may contribute to higher morbidity and mortality in this group of patients[27,28]. It is well-known that infection and critical illness are associated with development of TCM, which may explain the finding of a higher association with sepsis in our TCM cohort[29-31]. Nonetheless, it is unclear whether sepsis preceded the occurrence of TCM, given the limitations of the database utilized in this study.

Furthermore, we found an increasing prevalence of TCM in our studied population of OLT recipients between 2015 and 2020. This higher event rate may be attributed to the increasing numbers of patients undergoing OLT, and perhaps more importantly, better recognition and improved diagnosis of the syndrome. Additionally, data from observational studies reported that coronavirus disease 2019 (COVID-19) pandemic, which started in early 2020, may have contributed to the higher incidence of TCM[32-34]. The increased incidence was seen in both the general population and COVID-19 patients, which was linked to increased psychological distress as well as heightened sympathetic responses, cytokine storm, and microvascular dysfunction seen in COVID-19 patients[32]. The adverse effects on mental health may be consequences of social distancing, economic worry, and fear of contracting the virus, among other concerns. The association between COVID-19 and TCM may be explained by potential pathophysiological links between the two conditions. Though these direct connections are not fully understood, different mechanisms were proposed for this association. First, the heightened release of pro-inflammatory cytokines and chemokines seen in some COVID-19 patients can trigger myocardial injury that may lead to TCM[35]. Second, the increased sympathetic nervous system activity, noted in

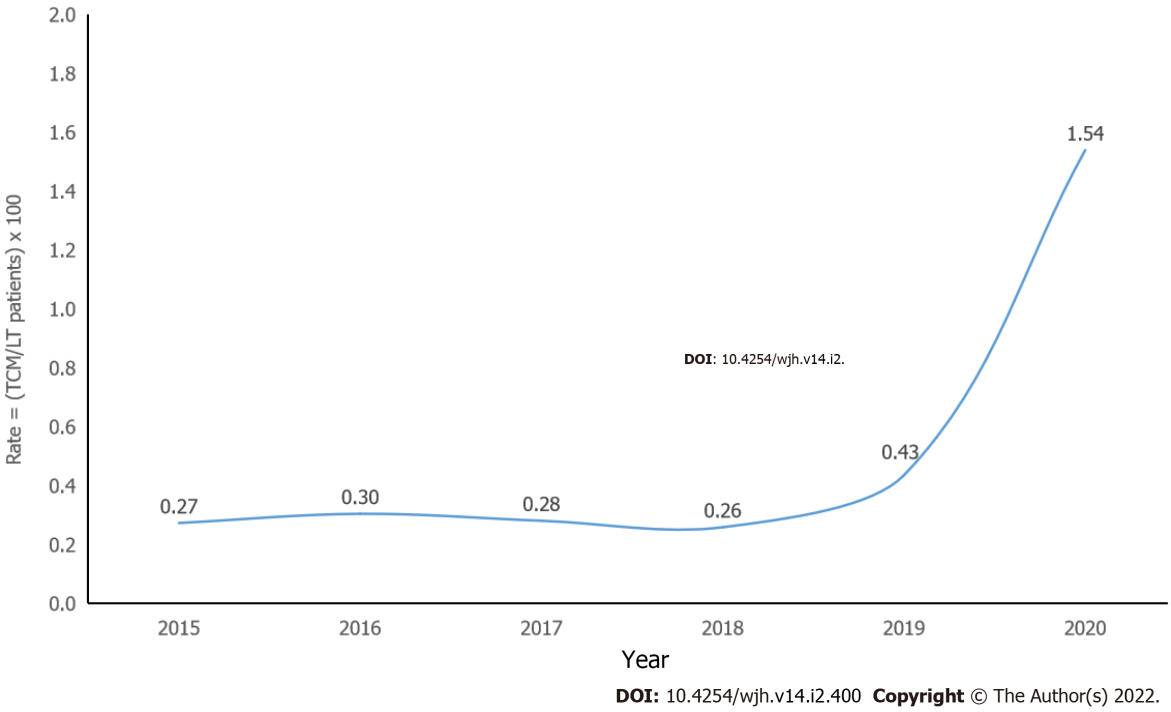

Figure 1 Rates of Takotsubo cardiomyopathy among liver transplant patients between 2015 and 2020. LT: Liver transplant; TCM: Takotsubo cardiomyopathy.

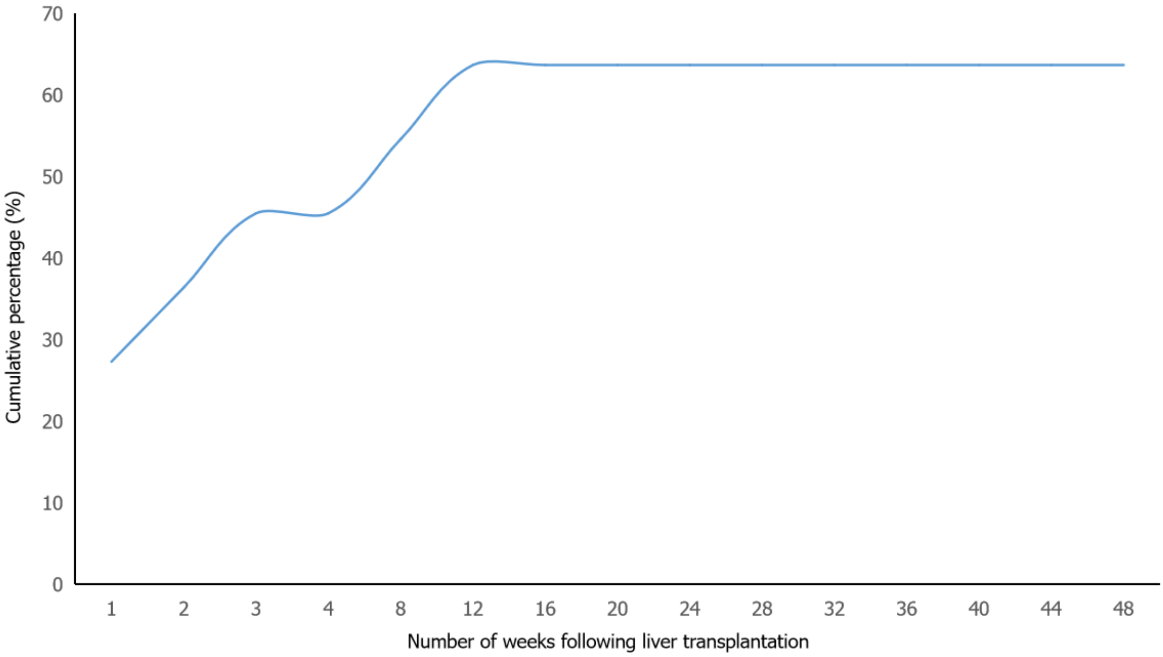

Figure 2 Timing of Takotsubo cardiomyopathy diagnosis after liver transplantation shown as the cumulative percentage of the total number of cases diagnosed in the study period (*n* = 110).

some COVID-19 patients, may result in a catecholamine-induced myocardial stunning, and subsequently stress-induced cardiomyopathy[36]. Last, microvascular dysfunction has been reported in some cases of COVID-19 infection and was attributed to virus-induced systemic inflammatory response and coagulopathy. This microvascular dysfunction has been proposed as a potential mechanism for COVID-associated TCM[37]. Previous reports have shown that patients with COVID-19 infection may demonstrate various histopathological findings on postmortem examinations, including but not limited to, myocyte necrosis, inflammatory cell infiltration, lymphocytic or eosinophilic myocarditis, among

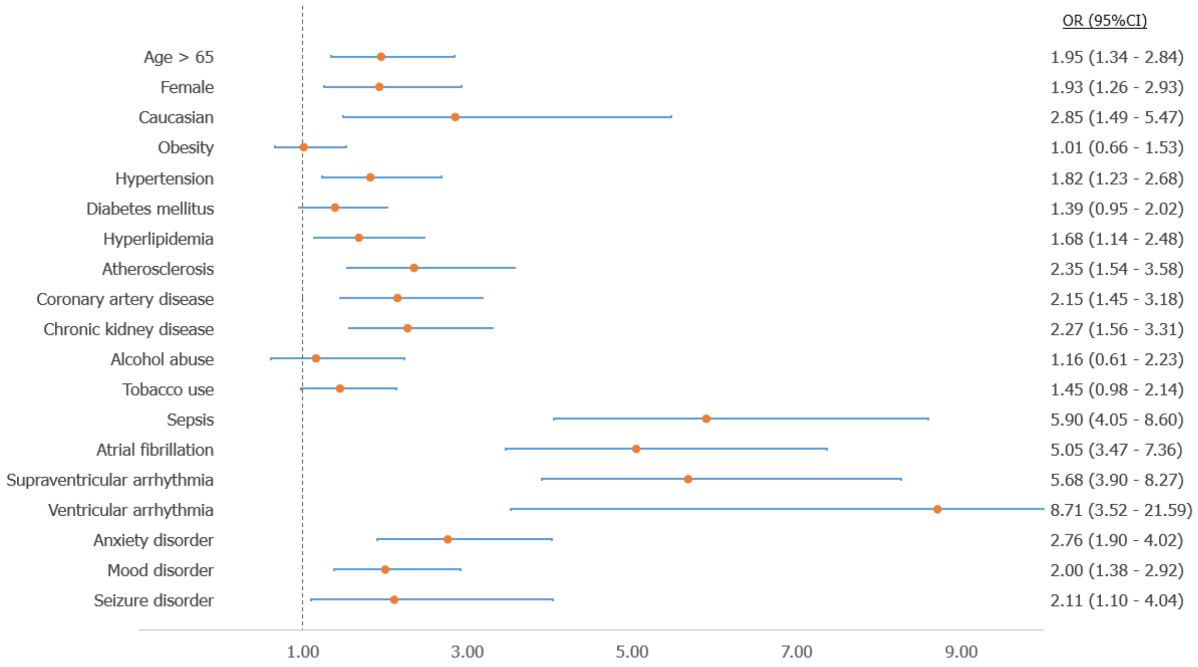

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Figure 3 Predictors of Takotsubo cardiomyopathy for liver transplant patients.

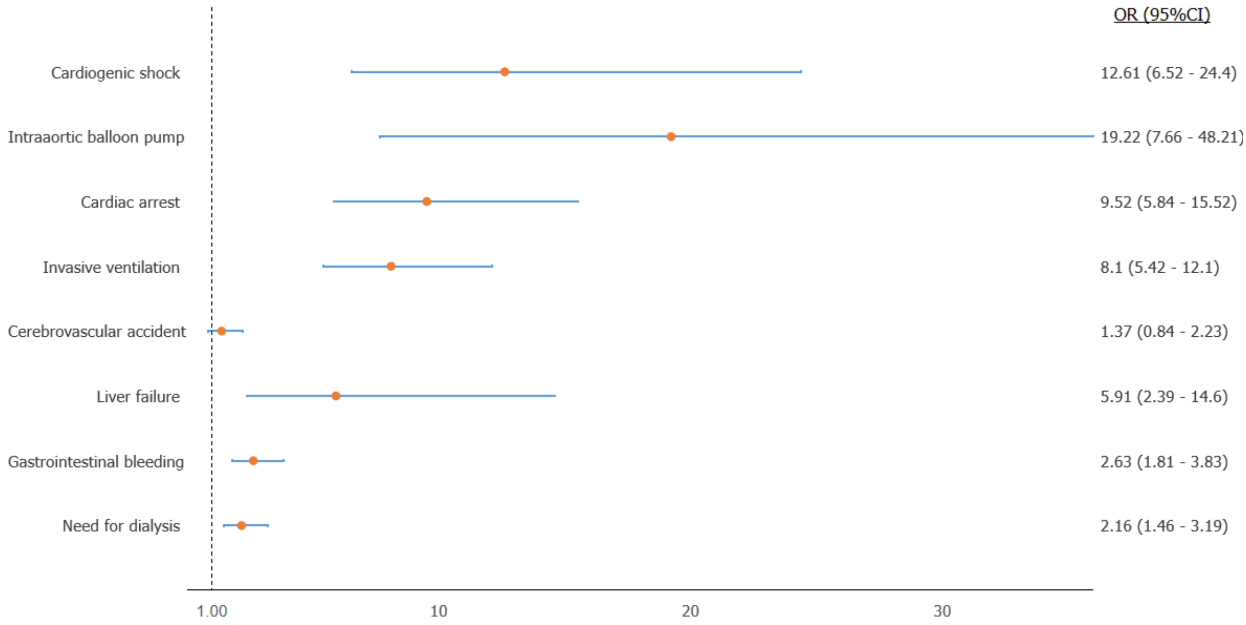

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Figure 4 Clinical outcomes for patients developing Takotsubo cardiomyopathy following liver transplant.

others[38]. Whether these findings are associated with, or increase the risk of, developing TCM remains largely unknown.

Another key finding in our study was that patients who developed TCM had significantly higher rates of life-threatening complications and adverse events, including cardiogenic shock, ventricular arrhythmias, cardiac arrest, respiratory failure requiring invasive mechanical ventilation, acute kidney injury requiring renal replacement therapy, as well as ischemic cerebrovascular accidents. These findings are consistent with prior reports of increased in-hospital complications among patients who developed TCM[1,39-41]. Nonetheless, the observed differences in baseline comorbidities between the two study groups of OLT recipients could also represent a driving factor for the higher in-hospital morbidity and adverse events presenting in patients who developed TCM. Regardless of the exact etiology and pathogenesis, recognition of TCM as a potential postoperative complication in OLT

recipients is pivotal, given its implications on patient outcomes with higher rates of in-hospital complications. Prior studies showed that despite a better recognition of the syndrome, short-term mortality rates remained relatively high[1].

There are several limitations to the current study due to the nature and well□described shortcomings of database studies. First, there is an inability to verify the accuracy of diagnoses or outcomes with potential errors in coding of diseases or procedures. Second, the database does not capture variables related to the severity of TCM (*e.g.*, left ventricular ejection fraction), cardiac-imaging data, use of antithrombotic agents or inotropes, and long-term outcomes. As the database also does not provide information regarding the temporal relationship between diagnoses, it is not possible to reliably distinguish in-hospital complications from comorbidities using this database. Third, owing to the observational nature, our study is subject to traditional biases, such as selection bias. Moreover, the differences reported during comparison of outcomes are subject to residual confounding. Fourth, the lack of follow-up data of patients limited our ability to report outcomes after hospital discharge for patients who developed TCM following OLT.

CONCLUSION

In conclusion, in this large, multicenter retrospective analysis of OLT recipients, transplant recipients had a higher rate of TCM occurrence compared to the general population. The majority of patients who developed TCM following OLT had higher rates of in-hospital complications, including cardiogenic shock, respiratory failure, ventricular arrhythmias, and the need for renal replacement therapy. Hence, TCM development among OLT patients contributes to significant patient morbidity and resource utilization. Multicenter, prospective studies focusing on risk factors and predictors of TCM in OLT recipients are required, in order to fully explore the factors responsible for this disease association and confirm the various outcomes observed in this patient population.

ARTICLE HIGHLIGHTS

Research background

Orthotopic liver transplant recipients are a particularly vulnerable patient population with an elevated risk of developing various complications. Takotsubo cardiomyopathy (TCM) is one of the complications that is thought to have an association with liver transplantation, and can impact the overall prognosis.

Research motivation

Limited data is available regarding the association between orthotopic liver transplantation and TCM. The current research study evaluated this proposed association, and investigated the predictors and outcomes in this specific patient population.

Research objectives

To study the association between orthotopic liver transplantation and TCM, provide details about the demographic characteristics of the patient cohort, and examine the factors that affect the development of TCM in liver transplant patients, with a focus on identifying predictive variables and associated outcomes.

Research methods

Using a multi-center database of de-identified electronic health record data, a cohort of patients who underwent orthotopic liver transplant during the study period was identified. The sample was investigated to reveal the subset of patients who developed TCM. The data was analyzed to evaluate the association of TCM and liver transplantation, and descriptive statistical methods were utilized to demonstrate the specific features pertaining to the cohort of interest.

Research results

The study revealed that TCM is more likely to develop in liver transplant recipients compared to non-recipients. Predictors for the development of this association are described, with older age, female gender, and Caucasian ethnicity being a few notable risk factors. The research study also showed a higher incidence of poor outcomes in liver transplant patients who develop TCM, including but not limited to, cardiogenic shock, cardiac arrest, and multi-organ failure.

Research conclusions

Liver transplant recipients are a vulnerable patient population who have a higher risk of developing TCM. The development of this cardiac complication is associated with a heightened rate of in-hospital

complications. Knowledge of preexisting risk factors may help identify high-risk patients, and can impact management decisions.

Research perspectives

Future multicenter, prospective research studies focusing on risk factors and predictors of TCM in orthotopic liver transplant recipients are required, in order to fully explore this disease association and confirm the various outcomes observed in this patient population.

FOOTNOTES

Author contributions: Zmaili M designed the research study and formulated the idea of the research topic, collected the data, wrote the manuscript, contributed to the statistical analysis and figure formatting; Alzubi J contributed to manuscript writing; Alkhayyat M contributed to manuscript writing, data collection, data analysis, and figure formatting; Cohen J contributed to manuscript writing and revision; Alkharabsheh S contributed to manuscript writing and revision, and data analysis; Rana M contributed to manuscript writing; Alvarez PA contributed to manuscript writing and revision; Mansoor E contributed to manuscript writing and revision; Xu B contributed to manuscript writing and revision, finalizing the research work.

Institutional review board statement: This study is based on a multicenter analytics and research platform developed by IBM Watson Health (Explorys Inc, Cleveland, OH, USA). At present, Explorys database is rich, integrated, and growing living clinical data set that is HIPAA-enabled, including more than 70 million unique patients across all 50 states in the United States, and thus provides a broad regional and climatic distribution of source population. Ethical review and informed consent were waived, since there are no identifiers associated with any of the patient data. The Explorys rounds cell counts to the nearest 10 and treats all cell counts between zero and 10 as equivalent in order to further protect the identities of patients. In other words, the identities of subjects is completely anonymous and there is no risk involved in the study. Additionally, the research presents no risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context.

Conflict-of-interest statement: This statement is to certify that all Authors have seen and approved the manuscript being submitted. We warrant that the article is the Authors' original work. We certify that there is no actual or potential conflict of interest in relation to this article to declare.

Data sharing statement: This study is based on a multicenter analytics and research platform developed by IBM Watson Health (Explorys Inc, Cleveland, OH, USA). At present, Explorys database is rich, integrated, and growing living clinical data set that is HIPAA-enabled, including more than 70 million unique patients across all 50 states in the United States, and thus provides a broad regional and climatic distribution of source population. Ethical review and informed consent were waived, since there are no identifiers associated with any of the patient data. The Explorys rounds cell counts to the nearest 10 and treats all cell counts between zero and 10 as equivalent in order to further protect the identities of patients. In other words, the identities of subjects is completely anonymous and there is no risk involved in the study. Additionally, the research presents no risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context.

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REFERENCES

1 **Templin C**, Ghadri JR, Diekmann J, Napp LC, Bataiosu DR, Jaguszewski M, Cammann VL, Sarcon A, Geyer V, Neumann CA, Seifert B, Hellermann J, Schwyzer M, Eisenhardt K, Jenewein J, Franke J, Katus HA, Burgdorf C, Schunkert H, Moeller C, Thiele H, Bauersachs J, Tschöpe C, Schultheiss HP, Laney CA, Rajan L, Michels G, Pfister R, Ukena C, Böhm M, Erbel R, Cuneo A, Kuck KH, Jacobshagen C, Hasenfuss G, Karakas M, Koenig W, Rottbauer W, Said SM, Braun-Dullaeus RC, Cuculi F, Banning A, Fischer TA, Vasankari T, Airaksinen KE, Fijalkowski M, Rynkiewicz A, Pawlak M, Opolski G, Dworakowski R, MacCarthy P, Kaiser C, Osswald S, Galiuto L, Crea F, Dichtl W, Franz WM, Empen K, Felix SB, Delmas C, Lairez O, Erne P, Bax JJ, Ford I, Ruschitzka F, Prasad A, Lüscher TF. Clinical Features and Outcomes of Takotsubo (Stress) Cardiomyopathy. *N Engl J Med* 2015; **373**: 929-938 [PMID: 26332547 DOI: 10.1056/nejmoa1406761]

2 **Kurisu S**, Sato H, Kawagoe T, Ishihara M, Shimatani Y, Nishioka K, Kono Y, Umemura T, Nakamura S. Tako-tsubo-like left ventricular dysfunction with ST-segment elevation: a novel cardiac syndrome mimicking acute myocardial infarction. *Am Heart J* 2002; **143**: 448-455 [PMID: 11868050 DOI: 10.1067/mhj.2002.120403]

3 **Dote K**, Sato H, Tateishi H, Uchida T, Ishihara M. [Myocardial stunning due to simultaneous multivessel coronary spasms: a review of 5 cases]. *J Cardiol* 1991; **21**: 203-214 [PMID: 1841907]

4 **Akashi YJ**, Goldstein DS, Barbaro G, Ueyama T. Takotsubo cardiomyopathy: a new form of acute, reversible heart failure. *Circulation* 2008; **118**: 2754-2762 [PMID: 19106400 DOI: 10.1161/CIRCULATIONAHA.108.767012]

5 **Wittstein IS**, Thiemann DR, Lima JA, Baughman KL, Schulman SP, Gerstenblith G, Wu KC, Rade JJ, Bivalacqua TJ, Champion HC. Neurohumoral features of myocardial stunning due to sudden emotional stress. *N Engl J Med* 2005; **352**: 539-548 [PMID: 15703419 DOI: 10.1056/nejmoa043046]

6 **Vitin AA**, Azamfirei L, Tomescu D. Perioperative Stress-Induced (Takotsubo) Cardiomyopathy in Liver Transplant Recipients. *J Crit Care Med (Targu Mures)* 2018; **4**: 56-63 [PMID: 30581996 DOI: 10.2478/jccm-2018-0006]

7 **Galván NT**, Kumm K, Kueht M, Ha CP, Yoeli D, Cotton RT, Rana A, O'Mahony CA, Halff G, Goss JA. Mending a Broken Heart: Treatment of Stress-Induced Heart Failure after Solid Organ Transplantation. *J Transplant* 2018; **2018**: 9739236 [PMID: 29670765 DOI: 10.1155/2018/9739236]

8 **Raval Z**, Harinstein ME, Skaro AI, Erdogan A, DeWolf AM, Shah SJ, Fix OK, Kay N, Abecassis MI, Gheorghiade M, Flaherty JD. Cardiovascular risk assessment of the liver transplant candidate. *J Am Coll Cardiol* 2011; **58**: 223-231 [PMID: 21737011 DOI: 10.1016/j.jacc.2011.03.026]

9 **Alqahtani SA**, Fouad TR, Lee SS. Cirrhotic cardiomyopathy. *Semin Liver Dis* 2008; **28**: 59-69 [PMID: 18293277 DOI: 10.1055/s-2008-1040321]

10 Solution Brief The IBM Explorys Platform Liberate your healthcare data [Internet]. [cited 2021 Jun 26]. Available from: https://www.ibm.com/downloads/cas/4P0QB9JN

11 US National Library of Medicine Unified Medical Language System (UMLS). Systematized Nomenclature of Medicine-Clinical Terms (SNOMED CT) [Internet]. [cited 2021 May 22]; Available from: https://www.nlm.nih.gov/healthit/snomedct/index.html

12 **Nelson SJ**, Zeng K, Kilbourne J, Powell T, Moore R. Normalized names for clinical drugs: RxNorm at 6 years. *J Am Med Inform Assoc* 2011; **18**: 441-448 [PMID: 21515544 DOI: 10.1136/amiajnl-2011-000116]

13 **Alkhayyat M**, Qapaja T, Aggarwal M, Almomani A, Abureesh M, Al-Otoom O, Zmaili M, Mansoor E, Abou Saleh M. Epidemiology and risk of psychiatric disorders among patients with celiac disease: A population-based national study. *J Gastroenterol Hepatol* 2021; **36**: 2165-2170 [PMID: 33554378 DOI: 10.1111/jgh.15437]

14 **Alkhayyat M**, Abureesh M, Almomani A, Abou Saleh M, Zmaili M, El Ouali S, Mansoor E, Rubio-Tapia A, Regueiro M. Patients With Inflammatory Bowel Disease on Treatment Have Lower Rates of Celiac Disease. *Inflamm Bowel Dis* 2021 [PMID: 34002219 DOI: 10.1093/ibd/izab084]

15 **Ashby D**. Practical statistics for medical research. Douglas G. Altman, Chapman and Hall, London, 1991. Stat Med [Internet] 1991 [cited 2021 Jun 25]; 10:1635-6 [DOI: 10.1002/sim.4780101015]

16 **Fede G**, Privitera G, Tomaselli T, Spadaro L, Purrello F. Cardiovascular dysfunction in patients with liver cirrhosis. *Ann Gastroenterol* 2015; **28**: 31-40 [PMID: 25608575]

17 **Åberg F**, Isoniemi H, Höckerstedt K. Long-term results of liver transplantation. *Scand J Surg* 2011; **100**: 14-21 [PMID: 21482501 DOI: 10.1177/145749691110000104]

18 **Jain A**, Reyes J, Kashyap R, Dodson SF, Demetris AJ, Ruppert K, Abu-Elmagd K, Marsh W, Madariaga J, Mazariegos G, Geller D, Bonham CA, Gayowski T, Cacciarelli T, Fontes P, Starzl TE, Fung JJ. Long-term survival after liver transplantation in 4,000 consecutive patients at a single center. *Ann Surg* 2000; **232**: 490-500 [PMID: 10998647 DOI: 10.1097/00000658-200010000-00004]

19 **Jadlowiec CC**, Taner T. Liver transplantation: Current status and challenges. *World J Gastroenterol* 2016; **22**: 4438-4445 [PMID: 27182155 DOI: 10.3748/wjg.v22.i18.4438]

20 **Moreno R**, Berenguer M. Post-liver transplantation medical complications. *Ann Hepatol* 2006; **5**: 77-85 [PMID: 16807513 DOI: 10.1016/s1665-2681(19)32022-8]

21 **Raval Z**, Harinstein ME, Skaro AI, Erdogan A, DeWolf AM, Shah SJ, Fix OK, Kay N, Abecassis MI, Gheorghiade M, Flaherty JD. Cardiovascular risk assessment of the liver transplant candidate. *J Am Coll Cardiol* 2011; **58**: 223-231 [PMID: 21737011 DOI: 10.1016/j.jacc.2011.03.026]

22 **Khera R**, Light-McGroary K, Zahr F, Horwitz PA, Girotra S. Trends in hospitalization for takotsubo cardiomyopathy in the United States. *Am Heart J* 2016; **172**: 53-63 [PMID: 26856216 DOI: 10.1016/j.ahj.2015.10.022]

23 **Deshmukh A**, Kumar G, Pant S, Rihal C, Murugiah K, Mehta JL. Prevalence of Takotsubo cardiomyopathy in the United States. *Am Heart J* 2012; **164**: 66-71.e1 [PMID: 22795284 DOI: 10.1016/j.ahj.2012.03.020]

24 **Lemor A**, Ramos-Rodriguez AJ, De La Villa R, Hosseini Dehkordi SH, Vazquez de Lara F, Lee S, Rodriguez Rivera M, Casso Dominguez A, Argulian E. Impact of gender on in-hospital outcomes in patients with Takotsubo syndrome: A nationwide analysis from 2006 to 2014. *Clin Cardiol* 2019; **42**: 13-18 [PMID: 30393886 DOI: 10.1002/clc.23109]

25 **El-Sayed AM**, Brinjikji W, Salka S. Demographic and co-morbid predictors of stress (takotsubo) cardiomyopathy. *Am J*

Cardiol 2012; **110**: 1368-1372 [PMID: 22819424 DOI: 10.1016/j.amjcard.2012.06.041]
26 **Vitale C**, Rosano GM, Kaski JC. Role of Coronary Microvascular Dysfunction in Takotsubo Cardiomyopathy. *Circ J* 2016; **80**: 299-305 [PMID: 26763468 DOI: 10.1253/circj.CJ-15-1364]
27 **Syed FF**, Asirvatham SJ, Francis J. Arrhythmia occurrence with takotsubo cardiomyopathy: a literature review. *Europace* 2011; **13**: 780-788 [PMID: 21131373 DOI: 10.1093/europace/euq435]
28 **Pant S**, Deshmukh A, Mehta K, Badheka AO, Tuliani T, Patel NJ, Dabhadkar K, Prasad A, Paydak H. Burden of arrhythmias in patients with Takotsubo cardiomyopathy (apical ballooning syndrome). *Int J Cardiol* 2013; **170**: 64-68 [PMID: 24207072 DOI: 10.1016/j.ijcard.2013.10.041]
29 **Vallabhajosyula S**, Deshmukh AJ, Kashani K, Prasad A, Sakhuja A. Tako-Tsubo Cardiomyopathy in Severe Sepsis: Nationwide Trends, Predictors, and Outcomes. *J Am Heart Assoc* 2018; **7**: e009160 [PMID: 30371194 DOI: 10.1161/JAHA.118.009160]
30 **Cappelletti S**, Ciallella C, Aromatario M, Ashrafian H, Harding S, Athanasiou T. Takotsubo Cardiomyopathy and Sepsis. *Angiology* 2017; **68**: 288-303 [PMID: 27303068 DOI: 10.1177/0003319716653886]
31 **Richard C**. Stress-related cardiomyopathies. *Ann Intensive Care* 2011; **1**: 39 [PMID: 21933374 DOI: 10.1186/2110-5820-1-39]
32 **Haft JW**, Atluri P, Ailawadi G, Engelman DT, Grant MC, Hassan A, Legare JF, Whitman GJR, Arora RC; Society of Thoracic Surgeons COVID-19 Task Force and the Workforce for Adult Cardiac and Vascular Surgery. Adult Cardiac Surgery During the COVID-19 Pandemic: A Tiered Patient Triage Guidance Statement. *Ann Thorac Surg* 2020; **110**: 697-700 [PMID: 32305286]
33 **Giustino G**, Croft LB, Oates CP, Rahman K, Lerakis S, Reddy VY, Goldman M. Takotsubo Cardiomyopathy in COVID-19. *J Am Coll Cardiol* 2020; **76**: 628-629 [PMID: 32517962 DOI: 10.1016/j.jacc.2020.05.068]
34 **Dweck MR**, Bularga A, Hahn RT, Bing R, Lee KK, Chapman AR, White A, Salvo GD, Sade LE, Pearce K, Newby DE, Popescu BA, Donal E, Cosyns B, Edvardsen T, Mills NL, Haugaa K. Global evaluation of echocardiography in patients with COVID-19. *Eur Heart J Cardiovasc Imaging* 2020; **21**: 949-958 [PMID: 32556199 DOI: 10.1093/ehjci/jeaa178]
35 **Figueiredo Neto JA**, Marcondes-Braga FG, Moura LZ, Figueiredo AMES, Figueiredo VMES, Mourilhe-Rocha R, Mesquita ET. Coronavirus Disease 2019 and the Myocardium. *Arq Bras Cardiol* 2020; **114**: 1051-1057 [PMID: 32638896 DOI: 10.36660/ABC.20200373]
36 **Chadha S**. 'COVID-19 pandemic' anxiety-induced Takotsubo cardiomyopathy. *QJM* 2020; **113**: 488-490 [PMID: 32311043 DOI: 10.1093/QJMED/HCAA135]
37 **Montone RA**, Iannaccone G, Meucci MC, Gurgoglione F, Niccoli G. Myocardial and Microvascular Injury Due to Coronavirus Disease 2019. *Eur Cardiol* 2020; **15**: e52 [PMID: 32617121 DOI: 10.15420/ECR.2020.22]
38 **Satturwar S**, Fowkes M, Farver C, Wilson AM, Eccher A, Girolami I, Pujadas E, Bryce C, Salem F, El Jamal SM, Paniz-Mondolfi A, Petersen B, Gordon RE, Reidy J, Fraggetta F, Marshall DA, Pantanowitz L. Postmortem Findings Associated With SARS-CoV-2: Systematic Review and Meta-analysis. *Am J Surg Pathol* 2021; **45**: 587-603 [PMID: 33481385 DOI: 10.1097/PAS.0000000000001650]
39 **Vallabhajosyula S**, Barsness GW, Herrmann J, Anavekar NS, Gulati R, Prasad A. Comparison of Complications and In-Hospital Mortality in Takotsubo (Apical Ballooning/Stress) Cardiomyopathy Versus Acute Myocardial Infarction. *Am J Cardiol* 2020; **132**: 29-35 [PMID: 32762963 DOI: 10.1016/j.amjcard.2020.07.015]
40 **Tsuchihashi K**, Ueshima K, Uchida T, Oh-mura N, Kimura K, Owa M, Yoshiyama M, Miyazaki S, Haze K, Ogawa H, Honda T, Hase M, Kai R, Morii I; Angina Pectoris-Myocardial Infarction Investigations in Japan. Transient left ventricular apical ballooning without coronary artery stenosis: a novel heart syndrome mimicking acute myocardial infarction. Angina Pectoris-Myocardial Infarction Investigations in Japan. *J Am Coll Cardiol* 2001; **38**: 11-18 [PMID: 11451258 DOI: 10.1016/S0735-1097(01)01316-X]
41 **Bybee KA**, Kara T, Prasad A, Lerman A, Barsness GW, Wright RS, Rihal CS. Systematic review: transient left ventricular apical ballooning: a syndrome that mimics ST-segment elevation myocardial infarction. *Ann Intern Med* 2004; **141**: 858-865 [PMID: 15583228 DOI: 10.7326/0003-4819-141-11-200412070-00010]

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