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ORIGINAL ARTICLE

Clinical features and three-year outcomes of Takotsubo (stress) cardiomyopathy: Observational data from one center

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Abstract *Objective:* The natural history, management, and outcome of Takotsubo (stress) cardiomyopathy (TTC) is not clear. The aim of this study was to investigate clinical features, define prognostic predictors, and assess the clinical course and outcomes of patients with TTC.
Methods: We analyzed 64 patients (52 women) meeting the proposed Mayo Clinic diagnostic criteria for TTC. All patients were treated at Vilnius University Hospital Santariskiu Klinikos from 2001-01-01 to 2014-11-27. Data were collected on the basis of medical records and follow-up data was collected by phone.
Results: The mean age of analyzed patients was 63.4 ± 14.6 years; the mean follow-up was 2.9 years. More than half of the patients (52%) did not have any clear stressful triggers. During admission, symptoms such as chest pain (64%) and general weakness (45%) were reported more often than other symptoms. Almost all patients (94%) had the classical TTC form; the remaining 6% of patients had "inverted" TTC. The mean left ventricular ejection fraction (LVEF) on admission was 37.7% (± 8.2%). A pseudonormal or restrictive pattern of LV filling, moderate to severe mitral regurgitation (MR), and right ventricular involvement were uncommon in the patients. The in-hospital course showed cardiogenic shock in 23% of the cases, resulting in the death of 5 (8%) patients. We discovered that only peak concentration of troponin I was a significant predictor of in-hospital mortality (HR 1.067, 95%CI 1.022–1.113, p=0.003). At the end of the follow-up period, 45 (87%) women and 8 (67%) men were alive. This makes the overall observed mortality at 3 years approximately 17.2%. Using multivariate analysis, elevation of BNP (HR for increase by 10 ng/l 1.002, 95%CI 1–1.003, p=0.022) and cardiogenic

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shock on admission (HR 8.696, 95%CI 1.198—63.124, p=0.032) were significant predictors of overall mortality. Other prognostic factors assessed on admission were nonsignificant predictors of overall mortality.
Conclusions: Our analysis shows that in-hospital mortality is influenced by the peak concentration of troponin I, and overall mortality is affected by cardiogenic shock and the elevation of BNP during admission. The assessment of troponin I and BNP can help with the prognostication of TTC patients in our daily clinical practice.

1. Introduction

Takotsubo cardiomyopathy (TTC), otherwise known as stress-induced cardiomyopathy, apical ballooning syndrome, or broken-heart syndrome, is a stress-induced disease. It is best described as a transient left ventricle (LV) systolic dysfunction. This cardiomyopathy was first reported in Japan in the 1990s and was named "takotsubo" ("octopus trap") because the shape of the LV looks like an octopus trap.[1] The incidence of this heart disease is not known, but it is considered responsible for 2% of all cases of acute coronary syndrome in the United States.[2] Sympathetic hyperexcitation is the most likely cause, but the pathogenic mechanism is still uncertain. Catecholamines are released in the bloodstream when the body anticipates a physical or emotional stressor. The high concentration of norepinephrine stimulates α_1 and β_1 receptors and triggers coronary vasospasm and the hypercontraction of basal segments. Simultaneously, a constant and high concentration of epinephrine stimulates β_2-receptors and switches them from stimulating G-proteins to inhibiting G-proteins, which results in apical dyskinesis.[3,4] There are a few types of TTC, depending on the pattern of left ventricle ballooning. Among cases with apical ballooning, two-thirds of all cases are typical, and one-third are atypical. The most common form among the latter group is midventricular ballooning. Other forms include diffuse ballooning and basal segment ballooning (also called the "inverse" or "artichoke" form[5,6]). For the diagnosis of this pathological condition, the proposed Mayo Clinic diagnostic criteria for TTC is more widely used (Table 1).[7]

This cardiomyopathy is quite new, thus there is a shortage of survival data and a lack of known prognostic predictors.[8,9] Numerous studies analyze short-term outcomes, but only a few perform a long-term survival analyses.[9,10] Also although there are many studies that analyze predictors for complications and outcomes, those studies are small, and the data are controversial.[8,11,12]

The goal of this study was to retrospectively analyze patients who were treated at one tertiary center and met the proposed Mayo Clinic diagnostic criteria for TTC.[7] The study investigates their a) clinical features and clinical course, b) short-term (in-hospital) and overall survival, and c) prognostic predictors.

2. Methods

We identified 79 patients meeting the proposed Mayo Clinic diagnostic criteria for TTC[7] who were treated at Vilnius University Hospital Santariskiu Klinikos from 2001-01-01 to 2014-11-27. All patients underwent echocardiography and invasive/non-invasive coronary angiography. A portion of the patients underwent cardiovascular magnetic resonance (CMR). All the data were collected from medical records. Follow-up data were collected by telephone interviews. Fifteen patients were excluded from the follow-up analysis because we were unable to contact them. A total of 64 patients were included in the final analysis. We used hospitalization period until in-hospital death or discharge to calculate in-hospital (short-term) survival and used the time period from discharge until death or last phone contact with the patient to calculate overall survival. Data were collected with the approval of the Lithuanian Bioethics Committee (No. 158200-13-576-178).

2.1. Statistical analysis

Variables were summarized with a mean and standard deviation (SD), median and interquartile range, or frequencies and percentages depending on the type, and the distribution of the variables. The Cox proportional hazards model was used to investigate the effect of several variables on survival. Each factor was assessed through separate univariate Cox regressions. The multivariate model was used in the presence of two or more significant predictors. A p value <0.05 was considered to indicate statistical significance. The data were analyzed using SPSS 20.0.

3. Results

In total, 64 patients that met the proposed Mayo Clinic diagnostic criteria for TTC were analyzed.

3.1. Clinical characteristics

The group consisted of 12 (19%) men and 52 (81%) women with a mean age of 63.4 ± 14.6 years (Table 2). The mean duration of treatment in our hospital was 12 (1—73) days. Stable patients without any complications and with

Table 1 Proposed Mayo clinic criteria for diagnosis of TTC (all four are required for the diagnosis).

1. Transient hypokinesis, akinesis, or dyskinesis in the left ventricular mid segments with or without apical involvement; the regional wall motion abnormalities extend beyond a single epicardial vascular distribution; a stressful trigger is often, but not always, present.
2. Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture.
3. New electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin.
4. Absence of pheochromocytoma and myocarditis.

recovery of LV function were transported to local hospitals for further treatment.

More than one-half of patients (33, 52%) did not have any clear stressful trigger; another 31 (48%) had either emotional or physical triggers (Table 2). On admission, symptoms such as chest pain (64%) and general weakness (45%) were reported more often than other symptoms such as dyspnea (22%), nausea/vomiting (14%) or heart palpitations (13%). The mean heart rate on admission was 93 bpm, and the mean blood pressure was 131/80 mmHg (Table 2).

Blood testing showed elevated concentrations of markers of myocardial damage and heart failure. The median concentration of brain natriuretic peptide (BNP) was 697.2 ng/l (299.5—1542.2); the normal value in the setting of acute heart failure is <100 ng/l). The median concentration of the creatinine kinase MB fraction was 8.0 μg/l (4.0—15.4; the normal range for women was <3.1 μg/l, for men was ≤5.2 μg/l); and the median concentration of troponin I was 2.2 μg/l (0.9—4.8; normal value <0.5 μg/l) (Table 2).

The admission electrocardiogram (ECG) revealed new electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) consistent with TTC in 51 (80%) patients and nonspecific alterations in 9 (14%) patients. ST and T changes on admission could not be evaluated in 4 (6%) patients due to ventricular tachycardia in one patient and pacemaker activity in three patients. Most of the patients had sinus rhythms on admission, however, eight (13%) patients had atrial fibrillation/flutter (Table 2).

Transthoracic echocardiography (TTE) was performed on all patients. TTE revealed that 60 patients (94%) had the classical TTC form; the remaining four (6%) patients had "inverted" or a so-called "artichoke" TTC form (Table 3). Diastolic dysfunction was evaluated in 61 (95%) patients and almost one half (41%) of them had slowed left ventricular relaxation, and the remaining 35 (59%) patients had no signs of diastolic dysfunction. Right ventricle involvement was observed in one (2%) patient. The majority of patients (92%) had trivial or mild mitral valve regurgitation (MR), and the remaining 5 (8%) patients had moderate to severe MR. The mean left ventricular ejection fraction (LVEF) on admission was 37.7 ± 8.2%. The TTE was performed again in 33 (52%) patients at discharge, and the mean LVEF had improved to 51.4 ± 6.3%.

Table 2 Clinical features of the study population. BNP — brain natriuretic peptide, SD — standard deviation, n — number, ECG — electrocardiogram, CT — computed tomography.

Clinical baseline characteristic	Values
Age, years (SD)	63.4 (14.6)
Female, n (%)	52 (81)
Duration of hospitalization, days	12 (1—73)
Triggering factor, n (%)	
Emotional stress	25 (39.1)
Physical stress	6 (9.4)
No identifiable trigger	33 (51.6)
Clinical presentation, n (%)	
Chest pain	41 (64.2)
General weakness	29 (45.3)
Dyspnea	14 (21.9)
Nausea/vomiting	10 (14.1)
Heart palpitations	8 (12.5)
Mean heart rate, bpm (SD)	92.7 (30.2)
Mean systolic/diastolic blood pressure, mmHg (SD)	131 (25.2)/80 (12.8)
Invasive coronary angiography, n (%)	55 (85.9)
No changes	52 (94.6)
Hemodynamically insignificant changes	3 (5.4)
Non-invasive CT coronary angiography, n (%)	9 (14.1)
No changes	9 (14.1)
Median troponin I, μg/l	2.2 (0.9—4.8)
Median BNP, ng/l	697.2 (299.5—1542.2)
Median creatinine kinase MB fraction, μg/l	8.0 (4.0—15.4)
ECG changes, n (%)	
Sinus rhythm	55 (85.9)
Atrial flutter/fibrillation	8 (12.5)
Ventricular tachycardia	1 (1.6)
Pacemaker rhythm	3 (4.7)
ST elevation	36 (56.2)
T inversion	15 (23.4)
Nonspecific changes	9 (14.1)

Fifty-five (86%) patients underwent invasive coronary angiography. Fifty-two (95%) of them had no coronary artery disease, and three (5%) had hemodynamically insignificant changes. Ventriculography was performed in 11 (20%) of patients, and all of them had basal segment hyperkinesis and apical akinesis. The remaining nine (14%) patients underwent non-invasive computed tomography (CT) coronary angiography because of low pre-test probability of coronary heart disease. All patients had normal coronary arteries without any changes (Table 2).

CMR was performed in 18 (28%) patients. Fourteen of the patients (77.8%) underwent CMR in the first week after the onset of symptoms, and all of them had contractile dysfunction typical for classical TTC. The remaining 4 patients underwent CMR at discharge. The mean LVEF as measured by CMR was 51.8 ± 2.5%, and apical edema on the T2 tirm sequence was present in 11 (61%) patients. There was no evidence of intraventricular thrombi in any of the 18

Table 3 Imaging (TTE and CMR) characteristics of the study population. SD — standard deviation, n — number, LVEF — left ventricular ejection fraction, LGE — late gadolinium enhancement.

Imaging characteristics	Values
TTE, n (%)	64 (100)
Typical TTC form, n (%)	60 (93.8)
Inverted or "artichoke" TTC form, n (%)	4 (6.3)
Mean LVEF, % (SD)	37.7 ± 8.2
Mean LVEF on discharge, % (SD)	51.4 ± 6.3
CMR, n (%)	18 (28.1)
Apical edema, n (%)	11 (61.1)
Absence of LGE, n (%)	12 (66.7)
Patchy LGE, n (%)	6 (33.3)

patients. The absence of late gadolinium enhancement (LGE) was observed in 12 (67%) patients and patchy LGE in injured segments (gray myocardium) was seen in six (33%) patients (Table 3, Fig. 1).

3.2. Short-term (in-hospital) survival

The hospital course was uneventful in 49 (76.6%) patients, but the remaining 15 (23.4%) patients exhibited cardiogenic shock. The other complications in acute phase were acute respiratory failure (4, 6%), ventricular tachycardia or ventricular fibrillation (3, 5%), asystole (5, 8%), and left ventricular outflow tract obstruction (4, 6%). There were (5, 8%) deaths during the hospitalization period (Table 4). Fifty-nine (92%) patients were successfully discharged from the hospital.

We found a strong positive correlation between hospital mortality and cardiogenic shock ($r=0.53$; $p<0.00001$). Nevertheless, using Cox regression analysis, only the peak concentration of troponin I was a significant predictor of in-hospital mortality (HR 1.067, 95%CI 1.022—1.113, $p=0.003$).

3.3. Overall survival

Contact with patients was obtained by phone 2.9 years (35.4, 5—87) months) after discharge. Fifty-nine patients were included in the overall survival analysis. At the end of follow-up, 53 (83%) of all analyzed patients were alive (45 women and 8 men), and 6 had died (3 women and 3 men). We found a weak positive correlation between the late mortality and the duration of hospitalization ($r=0.29$; $p=0.025$), a weak negative correlation between the late mortality and the absence of diastolic dysfunction on admission ($r=-0.3$; $p=0.019$), a weak negative correlation between the long-term survival and male gender ($r=-0.29$; $p=0.022$) and a moderate positive correlation between the late mortality and the peak BNP concentration on admission ($r=0.5$; $p=0.0001$). The overall survival analysis of all TTC patients is presented in Fig. 2. The general prognosis of TTC patients is good with a mortality rate of 17.2% in almost 3 years. All deaths occurred less than or equal to 32.2 months (2.7 years) after discharge, with most of the deaths (67%) occurring less than or equal to 7.2 months (half a year) after discharge.

Univariate Cox regression analysis showed that only the elevation of BNP by 10 units or more (HR for increase by 10 ng/l 1.001, 95%CI 1—1.002, $p=0.028$) and cardiogenic shock on admission (HR 7.516, 95%CI 2.181—25.898, $p=0.001$) were significant predictors of mortality. Using a multivariable model, the results were almost the same: the elevation of BNP (HR for increase by 10 ng/l 1.002, 95%CI 1—1.003, $p=0.022$) and cardiogenic shock on admission (HR 8.696, 95%CI 1.198—63.124, $p=0.032$) were significant predictors of mortality. Other prognostic factors, such as age, sex, heart rhythm and rate, LVEF, peak troponin concentration, MR severity, LV diastolic dysfunction, and right ventricular involvement were nonsignificant predictors of long-term mortality ($p>0.05$). TTC recurrence was observed in one woman, slightly over one year (14.2 months) after discharge.

4. Discussion

In this article, we present a comprehensive retrospective analysis of patients suffering from TTC at one tertiary Lithuanian center. This disease mostly affects women, who represent 89% of all patients diagnosed with TTC (81% in our study).[13] Postmenopausal women are the most vulnerable; 81% of all affected women are over 50 years of age. In 71% of cases, the disease is triggered by either emotional or

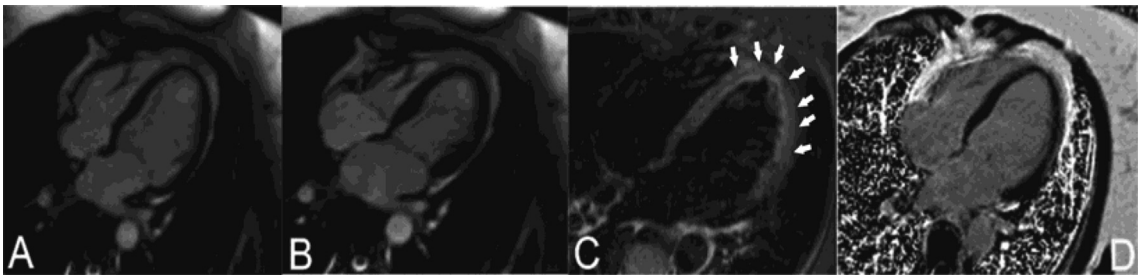

Figure 1 Typical CMR exam of the female patient suffering from TTC at discharge (recovery phase): A) end-diastolic cine 4 chamber heart view (balanced steady state free precession sequence), B) end-systolic cine 4 chamber heart view representing hyperkinesis of basal segments with impaired contraction of midventricular and apical segments (balanced steady state free precession sequence), C) 4 chambers heart view in T2 tirm sequence representing slight edema in midventricular and apical segments (arrows) and D) late gadolinium enhancement sequence showing the absence of LGE.

Table 4 The in-hospital complications. n — number, LVOTO — left ventricle outflow tract obstruction.

Complications during hospitalization	Value
In-hospital complications, n (%)	15 (23.4%)
Acute respiratory failure, n (%)	4 (6.3%)
Cardiogenic shock, n (%)	15 (23.4%)
Ventricular tachycardia or fibrillation, n (%)	3 (4.7%)
Asystole, n (%)	5 (7.8%)
LVOTO, n (%)	4 (6.3%)
Death, n (%)	5 (7.8%)

physical stressors. In our study, a clear trigger was recorded in 48% of cases. The most common emotional triggers are death of a loved one, relationship conflicts, fear, anger and anxiety.[14] The physical stressors that precede TTC include surgery and acute respiratory failure.[14] Most of the patients clinically mimic an acute coronary syndrome. The dominant symptom at presentation is chest pain. According to Singh K. et al., chest pain is found in 63.4% of patients. Our study showed similar results: 64% of the patients had chest pain. Dyspnea is the second most common symptom, affecting 23% of patients in the literature.[15] It affected 22% of cases in our study. The second most common symptom in our study was general weakness (45%). The admission electrocardiogram (ECG) revealed new with TTC consistent electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) in 51 (80%) patients involved in our study. Other studies have reported variable distributions of ECG changes: ST elevation in 49 (90%) of cases and T inversion in 44 (83%) patients. There are studies that show no ECG changes in 30% of cases.[16,17] Elevations in both troponin I and creatinine kinase MB fraction concentrations are typical for TTC. However, these levels do not correlate with the extension of myocardial damage and are usually higher in the setting of acute coronary syndromes. Notably, higher levels of BNP are usually found in TTC patients more than patients suffering from acute coronary syndromes.[18,19] According to the Mayo Clinic proposed TTC diagnostic criteria, cardiac catheterization should reveal no or minimal coronary artery disease.[7] This is consistent with our findings. In our study, we found that 95% of patients undergoing cardiac catheterization had normal coronary arteries, and almost 5% had hemodynamically insignificant or non-acute coronary changes. TTE revealed typical TTC changes: abnormal left ventricle morphology (apical ballooning, basal hyperkinesis, or inverted form), left ventricular wall motion abnormalities extending beyond a single epicardial vascular distribution, and resulting LV systolic dysfunction. Complications such as left ventricular outflow tract obstruction, moderate to severe MR, and thrombi in the left ventricular cavity may arise due to the above-described changes. In one TTC study, Citro et al. found mean LVEF in 37.5%, right ventricle involvement in 14.5%, LVOTO in 12.8%, and moderate to severe mitral valve regurgitation in 21.5% of cases.[20] Our results showed similar mean LVEF on admission (37.7%). However, other complications were not as common: right ventricle involvement was present in only 1.6%, LVOTO in 6.3%, and moderate to severe MR in 7.8% of patients.

TTC can be diagnosed and distinguished from other pathologies such as acute coronary syndrome or myocarditis using CMR. CMR shows specific regional wall motion abnormalities, edema matching the damaged area and, in most cases, no evidence of LGE. The absence of LGE is still debatable, and the presence of focal or patchy enhancement does not necessarily exclude TTC.[21] In their TTC

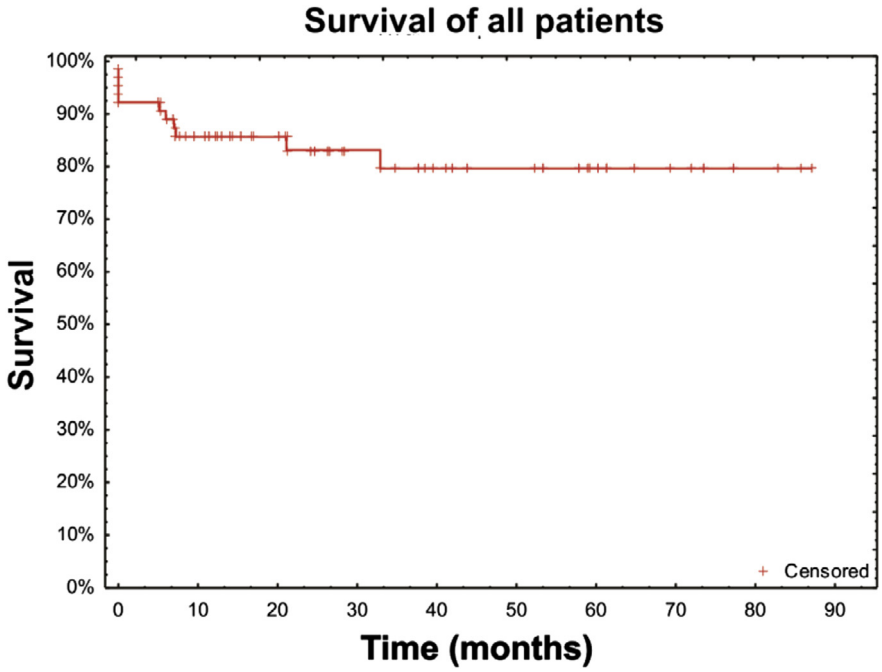

Figure 2 Kaplan — Meier curve of all-cause mortality in analyzed TTC cohort. The general prognosis of TTC patients is good, with a mortality rate of 17.2% in almost 2.9 years (follow-up from 5 through 87 months).

cohort, Eitel et al. found mean LVEF in 47.7%, right ventricle involvement in 34%, myocardial edema matching the damaged area in 81%, and focal or patchy LGE (using a threshold of 3 SD) in 9%.[14] Among our cohort, LVEF was slightly higher (51.8%). We believe this was because the MRI scans were performed approximately 4.71 ± 0.88 days after the onset of symptoms. Right ventricle involvement was observed in 5.6% of patients undergoing CMR scan. Myocardial edema was visible in 61% of patients, and patchy LGE was detected in 33% of patients. The most common complications that arise during the hospitalization of TTC patients are acute respiratory failure (5–13%), cardiogenic shock (11–19%), ventricular arrhythmias (3–4%), and death (0–8%).[5,11,12,14,15] Findings in our study were similar. We observed cardiogenic shock in 23%, acute respiratory failure in 6%, arrhythmias in 5%, and death in 8% of patients. According to the literature, the prognosis of TTC is good: 96% of all cases result in the complete recovery of myocardial function.[3] Long-term survival, as reported by the Swedish study, was similar to what was observed for myocardial infarction.[22] The recurrence rate ranges from 0–13%.[3,8,14] Our analysis also showed good overall prognosis, and at the end of our follow-up, 53 (83%) patients were alive (representing a mortality rate of 17.2% in almost three years of follow-up) (Fig. 2). As one of the main goals of our study was to investigate prognostic predictors in TTC, we found that only the peak concentration of troponin I significantly predicts in-hospital mortality ($p=0.003$). The significant predictors of overall mortality were the elevation of BNP ($p=0.022$) and cardiogenic shock on admission ($p=0.032$). Our data showed that we can use troponin I and BNP assessment for the prognostication of patients in our daily clinical practice.

5. Study limitations

The main limitation of our study is its retrospective nature; as a result, some data were unavailable. Fifteen patients dropped out of the study because we were unable to contact them. However, we found similar results when comparing ours with studies from around the world, and we do not think these patients would have changed our results significantly. Another drawback is the availability of CMR; we believe that if all patients had undergone scans, we would have been able to assess myocardial damage more thoroughly. Finally, because the mortality of TTC is low, it is difficult to establish statistically significant prognostic factors.

6. Conclusions

The overall analysis of patients treated at our tertiary care hospital from 2001 to 2014 showed that this cohort's clinical features, in-hospital survival and overall survival corresponded with data published in studies around the world. Our analysis shows that in-hospital mortality is influenced by the peak concentration of troponin I, and overall mortality is affected by cardiogenic shock and the elevation of BNP on admission. Overall survival in TTC patients is good. We think further analysis of genetic and molecular markers related to the prognostication of TTC patients is necessary. Additionally, multicenter TTC studies with larger sample sizes are needed to assess the prognostic factors for TTC.

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