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ORIGINAL RESEARCH

Characteristics and Outcomes of Patients With Takotsubo Syndrome: Incremental Prognostic Value of Baseline Left Ventricular Systolic Function

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BACKGROUND: We sought to determine (1) long-term outcomes in patients presenting with documented Takotsubo syndrome (TS), (2) whether left ventricular global longitudinal strain (LV-GLS) provides incremental prognostic value, and (3) prognostic cutoffs of LV ejection fraction (LVEF) and LV-GLS during an acute TS episode.

METHODS AND RESULTS: We studied 650 patients with TS (aged 66±14 years, 88% women) who were diagnosed clinically and angiographically between 2006 and 2018. Baseline LVEF and LV-GLS (using velocity vector imaging) were recorded. The primary end point was all-cause mortality. TS triggers were unknown (34%), emotional (16%), physical (41%), and neurologic (10%). Mean LVEF and LV-GLS were 36±10% and –11.6±0.4%; in addition, 94% patients had LVEF <52%, and 80% had apical ballooning. No patient had obstructive coronary artery disease. At a median of 2.2 years (interquartile range, 0.7–4.4), 175 (27%) had died (9% in-hospital deaths). Multivariate Cox survival analysis revealed that higher age (hazard ratio [HR], 1.35), male sex (HR, 1.75), lower baseline LVEF (HR, 1.02), worse LV-GLS (HR, 1.04), neurologic trigger (HR, 2.66), and physical trigger (HR, 2.64) were associated with mortality, whereas aspirin (HR, 0.70) and β-blockers (HR, 0.73) improved survival (all $P<0.049$). The addition of LVEF and LV-GLS to clinical markers (age, sex, cardiogenic shock at presentation, and peak troponin I) significantly increased log-likelihood ratios: clinical (–521.48), clinical plus LVEF (–511.32, $P<0.001$), and clinical plus LVEF and LV-GLS (–500.68, $P<0.001$). On penalized spline analysis, LVEF of 38% and LV-GLS of –10% were cutoffs below which survival was significantly worse.

CONCLUSIONS: Patients with TS with a neurologic or physical trigger had significantly worse survival than those without such a trigger, with baseline LVEF and LV-GLS providing incremental prognostic value.

Key Words: outcomes ■ strain ■ Takotsubo

Takotsubo syndrome (TS) is a relatively common condition with an estimated incidence between 15 to 30 cases per 100 000 person-years, and it is believed to represent 1% to 3% of all patients presenting with suspected acute coronary syndrome with ST-segment changes.[1-3] It results in transient left ventricular (LV) systolic dysfunction usually preceded by emotional or physical associated precipitating factors. The mechanism behind the development of TS remains elusive and controversial but is thought to be exaggerated sympathetic stimulation.[3] Furthermore, diagnosis of TS can be challenging because the clinical features of TS, such as chest pain, electrocardiographic changes, and biomarker elevation, tend to overlap with those of acute coronary syndrome,[1] myocarditis, and spontaneous coronary artery dissection.

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CLINICAL PERSPECTIVE

What Is New?

- In a large study of patients with Takotsubo syndrome, baseline left ventricular (LV) ejection fraction and global longitudinal strain provide independent and incremental long-term prognostic value in addition to standard clinical factors.
- An LV ejection fraction cutoff of 38% and an LV global longitudinal strain cutoff of –10% were associated with significantly worse survival.

What Are the Clinical Implications?

- Patients with Takotsubo syndrome have significantly worse long-term survival than an age- and sex-matched population.
- Relying on LV ejection fraction as a sole marker of cardiac functional improvement may not be an optimal strategy; more sensitive markers like LV global longitudinal strain may be needed to further risk stratify.
- Instituting appropriate long-term medical therapy and close follow-up is crucial to ensure improved long-term survival.

Nonstandard Abbreviations and Acronyms

HR	hazard ratio
IQR	interquartile range
LVEF	left ventricular ejection fraction
LV-GLS	left ventricular global longitudinal strain
sHR	subdistribution hazard ratio
TS	Takotsubo syndrome

Therefore, TS is diagnosed following a multistep process including echocardiographic findings of apical ballooning and wall motion abnormalities that extend beyond the territory perfused by a single coronary artery and the absence of culprit coronary artery disease lesions.[1,2] With the availability of long-term outcomes data, it is increasingly recognized that patients with TS have a long-term prognosis similar to patients with acute coronary syndrome and that poorer in-hospital and long-term prognoses (postdischarge 2-year mortality) are independently associated with age, lower ejection fraction, higher troponin leak, the presence of a physical trigger, atypical ballooning, cardiogenic shock, and cardiac arrest at presentation.[4-11]

In various cardiovascular disorders, we have previously demonstrated that LV ejection fraction (LVEF) alone may not completely reflect true regional function and that LV global longitudinal strain (LV-GLS) may be a more sensitive noninvasive method of assessing LV function and provide incremental prognostic value.[12-15] In the context of TS, a prior report demonstrated that both LVEF and LV-GLS are reduced during the acute phase.[16,17] However, these data did not demonstrate clinically relevant cutoffs of LVEF (and especially LV-GLS) that would be associated with future events. In addition, the incremental prognostic value of LV-GLS in this disease is uncertain. In this study, we sought (1) to assess the characteristics and factors associated with long-term outcomes in patients presenting with documented TS at a tertiary center, (2) to determine whether LV-GLS during an acute TS episode provides incremental prognostic value, and (3) to determine clinically meaningful cutoffs of LVEF and LV-GLS, obtained during an acute TS episode, that are associated with long-term outcomes.

METHODS

The authors will not make the data, analytic methods, and study materials available to other researchers.

Study Sample

This observational study sample consisted of 650 patients who presented to our center between 2006 and 2018 with acute chest pain syndrome. All patients were subsequently diagnosed with TS following a thorough clinical, echocardiographic, and coronary angiographic evaluation. These patients are part of an institutional review board–approved registry with a waiver of individual informed consent. TS was defined based on previously described criteria[6,18]: (1) a transient wall motion abnormality in the left ventricle extending beyond a single epicardial coronary artery distribution; (2) the absence of culprit obstructive coronary artery disease or angiographic evidence of acute plaque rupture, which could explain the wall motion abnormality; (3) new electrocardiographic abnormalities or elevation in cardiac troponin values; and (4) the absence of myocarditis. Based on the triggers of TS, patients were also divided into 4 subgroups: emotional, physical (eg, due to trauma, surgery, or medical diagnosis such as cancer), neurologic and unknown (for which the exact trigger could not be ascertained). Baseline clinical, imaging, and angiographic data, along with follow-up data, were manually extracted from electronic medical records.

Baseline, Predischarge, and Follow-Up Transthoracic Echocardiography

All patients underwent comprehensive transthoracic echocardiography at baseline, using commercial instruments (Philips Medical Systems; Siemens Medical Solutions; General Electric). LVEF (quantified

using a 2-dimensional biplane view), indexed LV dimensions, and left atrial area were measured at rest using quantitative techniques.[19] Severity of valvular regurgitation was ascertained using previously described standard techniques, based on established guidelines.[20] In addition, right ventricular systolic pressure was measured at rest.[21] The presence of severe wall motion abnormality in the apex and the distal LV walls, with resultant apical ballooning, was recorded.[1-3]

LV Global Longitudinal Strain

LV-GLS measurements were obtained from baseline transthoracic echocardiograms from gray-scale images of apical 2-, 3-, and 4-chamber views (A.A., N.I.). The frame rate was at least 30 frames/s. LV-GLS was analyzed offline using velocity vector imaging (Syngo VVI; Siemens), as described previously.[12] After manual definition of the LV endocardial border, the endocardium was automatically tracked throughout the cardiac cycle. LV-GLS was obtained by averaging all segmental strain values and later by averaging all 3 apical views. No patient was in atrial fibrillation at the time of analysis. Peak global strain was defined as peak negative value on the strain curve during the entire cardiac cycle. All measurements were made by investigators blinded to clinical and demographic information. As reported, LV-GLS values are negative; a lower absolute number represented a worse value than a higher number. Our group has previously provided data on reproducibility of LV-GLS measurements using the same software.[12,15]

Outcomes

For outcomes assessment, the date of an acute episode was defined as the beginning of the observational period (ie, initial presentation to the hospital). Mortality data were obtained from medical records or state and national databases (last queried February 2019). The primary outcome was all-cause mortality. In addition, the cause of death was ascertained as cardiac (including sudden cardiac death and acute congestive heart failure), documented noncardiac death, or unknown, after review of the records and/or discussion with the family. Sudden cardiac death was defined as unexpected sudden collapse occurring <1 hour from symptom onset in an otherwise stable patient. For the secondary end point, we included death (excluding documented noncardiac death due to cancer, liver failure, or primary respiratory or neurologic issues, but censoring at the time of event). Patients with an unknown cause of death were included as part of the secondary outcome unless their proximal history, just before death, strongly suggested a noncardiac cause.[22]

Statistical Analysis

Continuous variables are expressed as mean±SD or as median and interquartile range (IQR) for skewed distributions and were compared using the Student *t* test or ANOVA (for normally distributed variables) or the Mann–Whitney test (for nonnormally distributed variables). For comparative analysis, continuous variables (LVEF and LV-GLS) were divided into quartiles. Categorical data are expressed as percentages and compared using the χ^2 test or Fisher exact test, as appropriate. To test association between various relevant predictors and long-term primary events (all-cause mortality), we performed Cox proportional hazards analysis. The proportional hazards assumption was examined through inspection of Schoenfeld residuals plotted against time. Hazard ratios (HR) with 95% CIs were calculated and reported. In addition, receiver operating characteristic curve analysis was performed, and area under the curve was reported. Kaplan–Meier curves were generated to determine the cumulative proportion of patients (divided into quartiles of LVEF and LVGLS) with primary events as a function of time and were compared using the log-rank statistic or generalized Wilcoxon statistic, as appropriate. Because TS is an acute disease with upfront mortality, early survival times were given greater weight than long survival times. In addition, survival was compared with the survival of an age- and sex-matched US population (www.cdc.gov/nchs/products/life_tables). Because long-term cardiac and noncardiac deaths were competing risks, univariate and multivariate survival analysis was also performed using the competing risk regression analysis (Fine–Gray proportional subhazards model), and subdistribution HRs (sHR) were calculated, along with 95% CIs.[23,24] We also assessed the functional relationship between continuous variables (LVEF and LV-GLS) and the risk of all-cause death using penalized splines to estimate hazards in a Cox proportional hazards model. Relationship between exposure and response were described with the fitted splines and SE bars with HR on the *y*-axis and exposure on the *x*-axis. A rug plot is also displayed along the *x*-axis representing distribution of the underlying data. The discriminative ability of survival models for primary events were compared using log-likelihood ratios. Statistical analysis was performed using SPSS v11.5 (IBM Corp), and R 3.0.3 (R Foundation for Statistical Computing). $P<0.05$ was considered significant.

RESULTS

Baseline (initial presentation with TS) clinical, laboratory, electrocardiographic, and echocardiographic data for the whole study sample are shown in Table 1.

Table 1. Demographic and Clinical Data of the Entire Study Sample (n=650)

Variable	Total Population (n=650)	Triggers				
		Emotional (n=103)	Physical/Medical/ Procedural (n=266)	Neurologic (n=63)	Unknown (n=218)	*P* Value
Clinical and demographic data at initial hospitalization						
Age, y	66±14	65±12	66±14	65±13	66±13	0.168
Female sex	573 (88)	91 (88)	229 (86)	53 (84)	200 (92)	0.193
Race						
White	529 (81)	84 (82)	215 (81)	48 (76)	184 (84)	0.322
Black	93 (14)	15 (15)	35 (13)	14 (22)	29 (13)	
Other	28 (4)	4 (4)	16 (6)	1 (2)	7 (3)	
Body surface area, m^2	2.0±0.3	2.1±0.3	2.0±0.4	2.0±0.4	2.1±0.3	0.319
Hypertension	463 (71)	73 (71)	195 (73)	53 (84)	142 (65)	0.018
Diabetes mellitus	168 (26)	29 (28)	72 (27)	19 (30)	48 (22)	0.434
Hyperlipidemia	331 (51)	62 (60)	139 (52)	29 (46)	101 (46)	0.102
Smoker	171 (26)	32 (31)	62 (23)	22 (35)	55 (25)	0.168
Stroke	64 (10)	7 (7)	23 (7)	21 (33)	13 (6)	<0.001
Chronic renal failure	82 (13)	9 (9)	43 (16)	8 (13)	22 (10)	0.133
Atrial fibrillation	112 (17)	13 (13)	56 (21)	12 (19)	31 (14)	0.124
Previous cancer	133 (21)	18 (18)	106 (40)	7 (11)	2 (0.9)	<0.001
Psychiatric history	123 (19)	47 (46)	40 (15)	16 (25)	20 (9)	<0.001
Presenting symptoms at initial hospitalization						
Chest pain	342 (53)	77 (75)	124 (47)	9 (14)	132 (61)	<0.001
Dyspnea	331 (51)	63 (61)	142 (53)	25 (40)	101 (46)	0.014
Syncope	53 (8)	10 (10)	19 (7)	13 (21)	11 (5)	0.001
Cardiogenic shock	50 (8)	5 (5)	33 (12)	5 (8)	7 (3)	<0.001
ECG, laboratory and echocardiographic data at initial hospitalization						
ECG changes						
None	55 (9)	12 (12)	22 (8)	5 (8)	16 (7)	
Nonspecific STT wave changes	418 (64)	58 (56)	172 (65)	40 (64)	148 (68)	0.523
ST depression	38 (6)	9 (9)	15 (6)	6 (10)	8 (4)	
ST elevation	139 (21)	24 (23)	57 (21)	12 (19)	46 (21)	
Serum hemoglobin, mg/dL	12±3	13±4	12±4	12±3	12±4	0.289
Serum creatinine, mg/mL	1.1±1	1.1±1	1.2±1	1.2±1	1.1±1	0.274
Total cholesterol, mg/dL	165±50	169±40	172±52	175±54	169±51	0.321
Low-density lipoprotein, mg/dL	88±41	84±39	89±45	92±32	90±27	0.134
High-density lipoprotein, mg/dL	54±20	49±22	55±23	54±23	55±19	0.223
Triglycerides, mg/dL	120±96	114±82	127±89	122±93	118±79	0.192
Brain natriuretic peptide, pg/mL	160 (57–452)	152 (49–389)	174 (63–419)	177 (48–475)	165 (50–483)	0.229
Peak troponin I, ng/mL	0.22 (0.04–0.55)	0.19 (0.02–0.43)	0.25 (0.06–0.62)	0.29 (0.09–0.69)	0.21 (0.02–0.49)	0.122
LVEF, %	36±10	37±9	36±9	36±10	37±9	0.144
LVEF <52%	613 (94)	95 (92)	256 (96)	60 (95)	202 (93)	0.278
Indexed LV mass, g/m^2	82±32	81±29	77±30	89±38	84±35	0.209
LV-GLS, %	–11.6±0.4	–11.9±0.4	–11.5±0.4	–11.1±0.4	–11.7±0.4	0.402
LV-GLS worse than –18%	650 (100)	103 (100)	266 (100)	63 (100)	218 (100)	0.991
Indexed LVESD, cm/m^2	1.9±0.3	1.8±0.3	2.0±0.3	2.1±0.3	1.9±0.3	0.233
Apical ballooning	520 (80)	80 (81)	232 (90)	54 (87)	154 (87)	0.179
Indexed LA diameter, cm/m^2	2.1±0.4	2.1±0.4	2.2±0.4	2.0±0.4	2.2±0.3	0.339
≥II+ mitral regurgitation	58 (9)	88 (8)	24 (9)	6 (9)	20 (9)	0.528

(*Continued*)

Table 1. Continued

Variable	Total Population (n=650)	Triggers				
		Emotional (n=103)	Physical/Medical/ Procedural (n=266)	Neurologic (n=63)	Unknown (n=218)	*P* Value
≥II+ tricuspid regurgitation	69 (11)	11 (11)	27 (10)	7 (11)	24 (11)	0.589
RVSP, mm Hg	37±12	35±12	38±12	37±13	37±11	0.112
Medications at discharge after initial hospitalization						
Aspirin	437 (67)	61 (59)	193 (73)	44 (70)	139 (64)	0.048
β-Blockers	409 (63)	61 (63)	176 (66)	40 (63)	133 (61)	0.089
Statins	309 (48)	43 (42)	138 (52)	29 (46)	99 (45)	0.284
ACEI/ARB	341 (53)	46 (45)	144 (54)	39 (62)	112 (51)	0.159
Diuretics	189 (29)	30 (30)	80 (30)	20 (32)	59 (27)	0.123

Continuous variables are expressed as mean±SD or median (interquartile range) for skewed distributions and compared using the Student *t* test or ANOVA (for normally distributed variables) or the Mann–Whitney test (for nonnormally distributed variables). Otherwise, data are shown as count (percentage). ACEI indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; LA, left atrial; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; LV-GLS, left ventricular global longitudinal strain; and RVSP, right ventricular systolic pressure.

Overall, 613 (94%) patients had LVEF <50% at baseline, whereas 100% had LV-GLS worse than –18%. Median baseline LVEF and LV-GLS were 37% (IQR, 30%–45%) and –11.7% (IQR, –9.2 to –13.3%), respectively. The total study sample was broken down into 4 subgroups based on different TS triggers: emotional, physical, neurologic, and unknown. The baseline data in these subgroups are also shown in Table 1. Hypertension and stroke were most common in the neurologic trigger subgroup, whereas psychiatric and cancer histories were more commonly observed in the emotional and physical trigger subgroups, respectively. In terms of presenting symptoms, chest pain and dyspnea were most commonly observed in the emotional trigger subgroup, whereas syncope and shock were more commonly observed in the neurologic and physical trigger subgroups, respectively. Other clinical, laboratory, ECG, and echocardiographic variables were similar in all 4 subgroups.

There were 58 (9%) deaths during index hospitalization for TS, with no significant differences within subgroups (emotional [n=9, 9%], physical [n=27, 10%], neurologic [n=7, 11%], and unknown [n=15, 7%]). Of the 50 patients who presented with cardiogenic shock, 12 (24%) died during the index hospitalization; the rest recovered and were discharged.

At 30-days after discharge, 309 patients returned for a follow-up echo with improvement of median LVEF to 58% (IQR, 55–62). In this subgroup, only 40 (13%) had persistent LVEF <50%, of which 12 (30%)

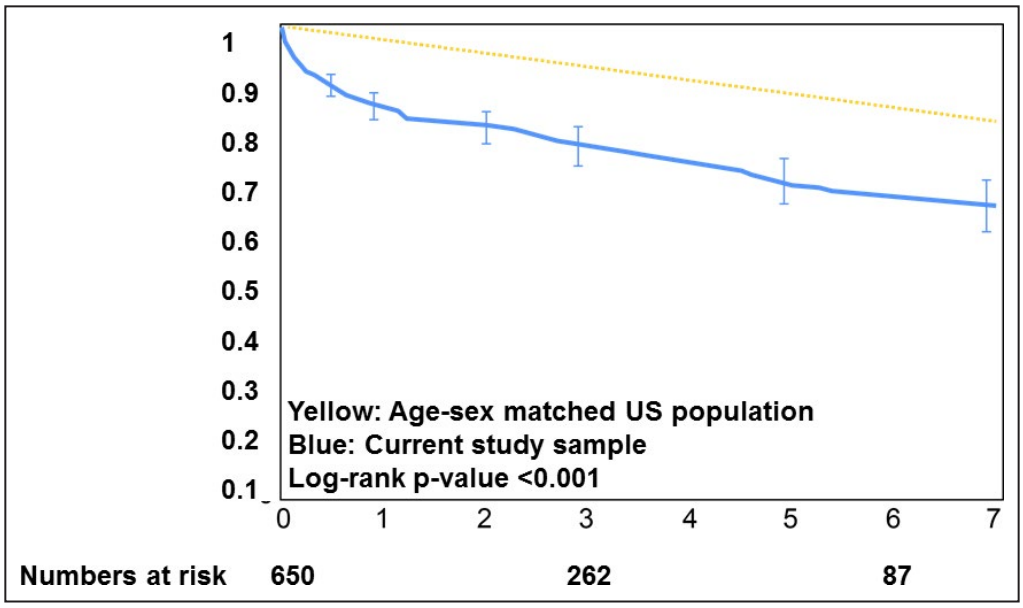

Figure 1. Kaplan–Meier survival curves of the entire study sample compared with a US age- and sex-matched population.

Table 2. Univariate and Multivariate Cox Proportional Hazards Analysis of Baseline Factors Associated With Long-Term All-Cause Mortality

Variable	Univariate		Multivariate	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age (for 10-y increase)	1.35 (1.20–1.52)	<0.001	1.35 (1.17–1.55)	<0.001
Male sex	1.82 (1.22–2.72)	0.003	1.75 (1.06–2.89)	0.032
Hypertension	1.40 (0.92–2.14)	0.144		
Hyperlipidemia	1.07 (0.79–1.45)	0.648		
Diabetes mellitus	1.36 (0.91–2.03)	0.148		
Triggers				
Unknown (reference)				
Emotional	1.14 (0.66–2.01)	0.623	1.21 (0.59–2.48)	0.601
Physical	2.45 (1.40–4.28)	0.001	2.64 (1.63–4.20)	<0.001
Neurologic	2.78 (1.90–4.01)	<0.001	2.66 (1.35–5.26)	<0.001
β-Blockers	0.65 [0.44–0.95]	0.022	0.73 (0.49–0.98)	0.038
ACEI/ARB	0.81 (0.32–1.99)	0.283		
Statins	0.86 (0.29–2.53)	0.391		
Aspirin	0.68 (0.45–0.92)	0.009	0.70 (0.48–0.94)	0.017
Peak troponin I at presentation	1.41 [1.23–1.63])	<0.001	1.31 [1.13–1.48])	<0.001
Baseline LVEF (continuous variable)*	1.03 (1.01–1.04)	<0.001	1.02 (1.01–1.04)	0.023
Worse baseline LV-GLS (continuous variable)†	1.07 (1.03–1.12)	0.004	1.04 (1.01–1.14)	0.032
Apical ballooning	1.12 [0.72–1.74]	0.604		
Baseline RVSP	1.31 (1.16–1.48)	<0.001	1.13 (0.98–1.27)	0.068
Cardiogenic shock at initial presentation	2.16 (1.36–3.42)	0.001	1.99 (1.19–2.98)	0.001

To test association between various relevant predictors and longer-term primary events (all-cause mortality), Cox proportional hazards analysis was performed. On receiver operating characteristic curve analysis, the area under the curve for multivariable analysis was 0.772, *P*<0.001. ACEI indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; LVEF, left ventricular ejection fraction; LV-GLS, left ventricular global longitudinal strain; and RVSP, right ventricular systolic pressure.

*Findings were similar if LVEF was used as a categorical variable at a cutoff of 35%.

†The interaction term between LVEF and LV-GLS was significant. The findings were similar if LV-GLS (continuous variable) was substituted for LVEF (continuous variable) in multivariate analysis.

died during follow-up. None of these patients had a documented concomitant nonischemic cardiomyopathy (32 patients were confirmed by cardiac magnetic resonance).

Survival Analysis

At a median follow-up of 2.2 years (IQR, 0.73–4.4), an additional 117 patients died, with total mortality observed in 175 (27%) patients. The long-term survival of the study sample was significantly worse than the survival of an age- and sex-matched US population, as shown in Figure 1. The breakdown of deaths was as follows: cardiac (n=74), documented noncardiac (n=78), and unknown but suspected cardiac (n=23). Univariate Cox proportional hazards analysis demonstrating the association between various potential factors and all-cause mortality is shown in Table 2. Based on that analysis, we subsequently performed a multivariate Cox proportional hazards analysis that demonstrated independent associations of higher long-term secondary outcomes with initial presentation of advanced age (HR, 1.35 [95% CI, 1.17–1.55]), male sex (HR, 1.75 [95% CI, 1.06–2.89]), physical trigger (HR, 2.64 [95% CI, 1.63–4.20]), neurologic trigger (HR, 2.66 [95% CI, 1.35–5.26]), cardiogenic shock (HR, 1.99 [95% CI, 1.19–2.98]), higher peak troponin I (HR, 1.31 [95% CI, 1.13–1.48]), lower LVEF (HR, 1.02 [95% CI, 1.01–1.04]), and worse LV-GLS (HR, 1.04 [95% CI, 1.01–1.14]). In contrast, use of a β-blocker (HR, 0.73 [95% CI, 0.49–0.98]) or aspirin (HR, 0.70 [95% CI 0.48–0.94]) was associated with low long-term secondary outcomes (all *P*<0.049). Sequential addition of LVEF and LV-GLS to clinical markers (age, sex, cardiogenic shock at presentation, and peak troponin I) significantly increased the log-likelihood ratios: clinical (–521.48), clinical plus LVEF (–511.32, *P*<0.001), and clinical plus LVEF and log-likelihood ratio (–500.68, *P*<0.001).

Long-term survival was better in the subgroups with emotional and unknown triggers (20/103 [19%] and 39/218 [18%], respectively) than among those with physical and neurologic triggers (96/266 [36%] and 20/63 [32%], respectively; log-rank statistic *P*<0.001). Kaplan–Meier survival curves of the total study sample,

separated into 4 trigger-based subgroups, are shown in Figure 2.

Subsequently, we also performed long-term survival analysis in the study sample, divided into quartiles of baseline LVEF and LV-GLS. Long-term mortality of the study sample based on baseline LVEF was significantly different for various quartiles (generalized Wilcoxon statistic, *P*<0.001; Figure 3): quartile 1 (LVEF >45%), 32 of 202 (16%); quartile 2 (LVEF 38%–45%), 34 of 129 (26%); quartile 3 (LVEF 30%–37%), 61 of 187 (33%); quartile 4 (LVEF <30%), 48 of 132 (36%). As shown in penalized spline analysis (Figure 4), LVEF of 38% was an optimal cutoff below which long-term survival was significantly worse in the study sample.

Similarly, long-term mortality of the study sample based on baseline LV-GLS was significantly different for various quartiles (generalized Wilcoxon statistic, *P*<0.001; Figure 5): quartile 1 (LV-GLS better than –13.3%), 36 of 162 (22%), quartile 2 (LV-GLS between –11.7% and –13.3%), 43 of 166 (26%); quartile 3 (LV-GLS between –9.2% and –11.7%), 34 of 161 (21%); quartile 4 (LV-GLS worse than –9.2%), 62 of 161 (39%). In addition, as shown in penalized spline analysis (Figure 6), baseline LV-GLS of –10% was an optimal cutoff below which long-term survival was significantly worse in the study sample.

Results of univariate and multivariate competing risk regression analysis showing data on association of various predictors with secondary outcome (deaths excluding documented noncardiac deaths) are shown in Table 3. Advanced age (sHR, 1.18 [95% CI, 1.07–1.42]), male sex (sHR, 1.39 [95% CI, 1.03–2.24]), physical trigger (sHR, 1.47 [95% CI, 1.06–373]), neurologic trigger (sHR, 1.52 [95% CI, 1.05–3.49]), cardiogenic shock (sHR, 2.12 [95% CI, 1.28–2.83]), higher peak troponin I (sHR, 1.27 [95% CI, 1.10–1.38]), lower LVEF (sHR, 1.02 [95% CI, 1.01–1.04]), and worse LV-GLS (sHR, 1.04 [95% CI, 1.01–1.11]) at initial presentation were independently associated with higher long-term secondary outcomes, whereas use of a β-blocker (sHR, 0.71 [95% CI, 0.51–0.97]) or aspirin (sHR, 0.68 [95% CI, 0.41–0.95]) was associated with low long-term secondary outcomes (all *P*<0.049).

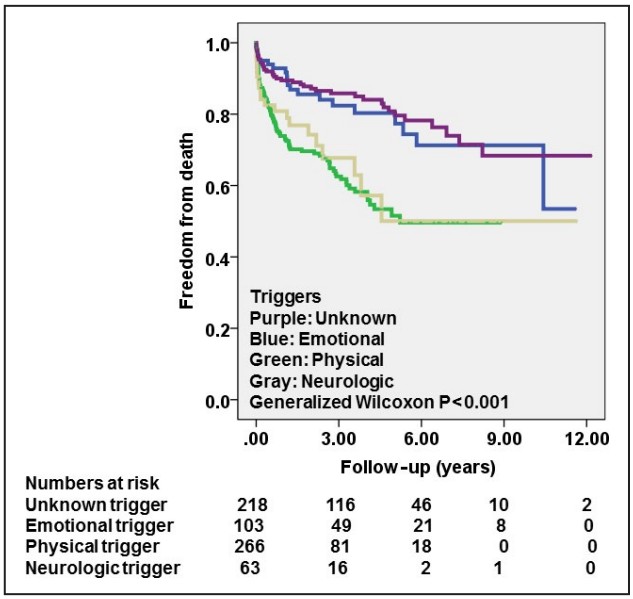

Figure 2. Kaplan–Meier survival curves of the entire study sample, separated on the basis of presenting triggers for Takotsubo syndrome.

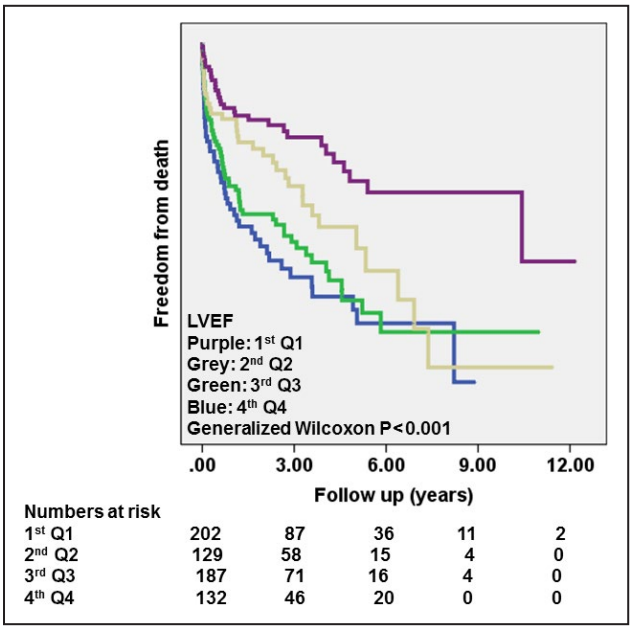

Figure 3. Kaplan–Meier survival curves of the entire study sample, separated on the basis of baseline left ventricular ejection fraction (LVEF) quartiles (Q): Q1, LVEF >45%; Q2, LVEF 38% and 45%; Q3, LVEF 30% and 37%; and Q4, LVEF <30%.

DISCUSSION

In this study, we described the clinical and echocardiographic characteristics of patients who presented with a documented diagnosis of TS to our tertiary care center. The major findings were as follows: (1) 58% of patients had either an emotional or a physical trigger for TS, whereas a definite trigger could not be identified in 35% of patients; (2) almost 9% of patients died during the index hospitalization (including 25% who presented with cardiogenic shock), with 12% annual mortality at a median follow-up of 2.2 years; (3) significantly higher observed long-term all-cause and cardiac mortality was noted in patients with physical and neurologic triggers versus those with emotional or unknown triggers; (4) baseline LVEF and LV-GLS provided incremental prognostic value for long-term mortality.

We were not able to identify a definite trigger in almost one third of the patients—similar to a prior

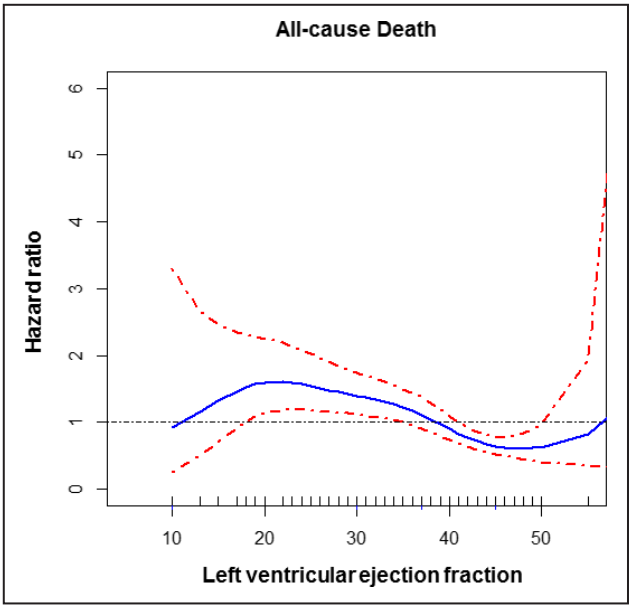

Figure 4. Penalized spline in the entire study sample, demonstrating the relationship between temporal changes in left ventricular ejection fraction (LVEF).
It demonstrates that an LVEF cutoff of ≈38% was associated with better long-term survival. Abnormal cutoff is assumed if the hazard ratio of 1 is crossed.

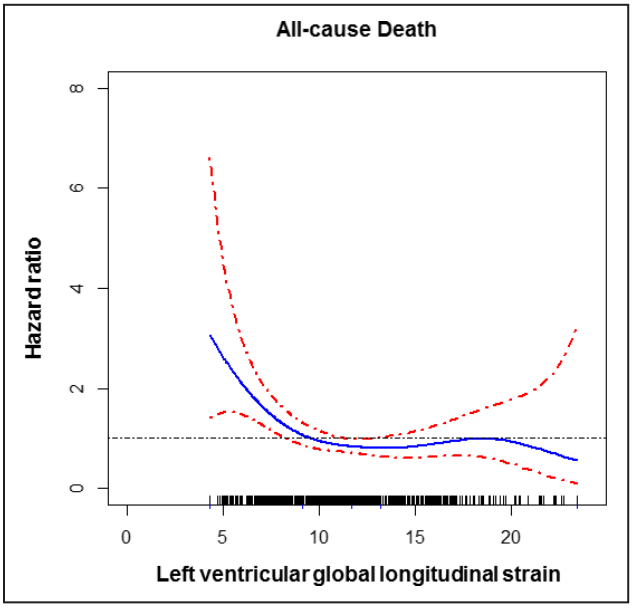

Figure 6. Penalized spline in the entire study sample, demonstrating the relationship between temporal changes in left ventricular global longitudinal strain (LV-GLS).
It demonstrates that an LV-GLS cutoff of approximately –10% was associated with better long-term survival. Abnormal cutoff is assumed if the hazard ratio of 1 is crossed.

report[11]—and the findings of improved long-term survival with an emotional (and unknown) trigger versus a neurologic (and physical) trigger were also similar. In addition, similar to previous reports, standard risk factors such as older age, male sex, cardiogenic shock, high peak troponin, and low baseline LVEF were associated with increased long-term mortality. Mortality was higher in the current study than previously reported,[7,11] likely because a significantly higher proportion of patients in the current study (8%) had cardiogenic shock at presentation versus the previous reports (4%). However, the mortality rate in the current study (12% per year) was not significantly different from a previous report (10% per year) when the proportion of patients with cardiogenic shock at the time of presentation was similar.[6] We also demonstrated that β-blocker and aspirin use, and not angiotensin receptor modulation, were associated with improved long-term survival.

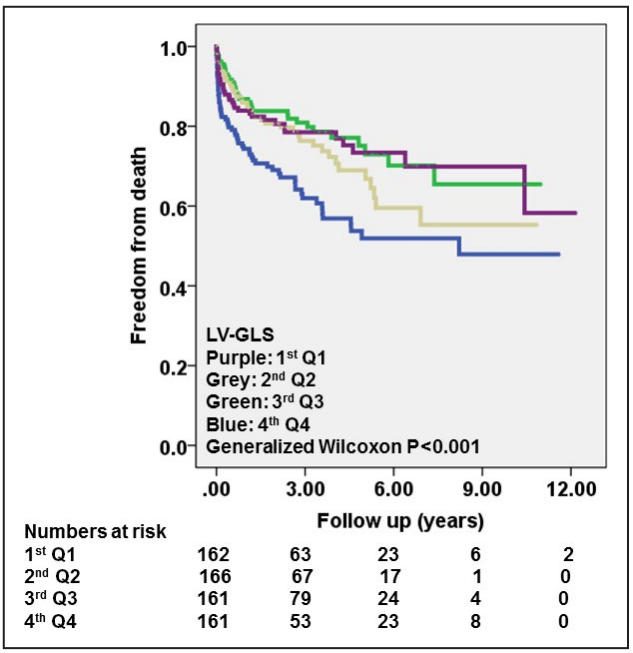

Figure 5. Kaplan–Meier survival curves of the entire study sample, separated on the basis of baseline left ventricular global longitudinal strain (LV-GLS) quartiles (Q): Q1, LV-GLS better than –13.3%; Q2, LV-GLS between –11.7% and –13.3%; Q3, LV-GLS between –9.2% and –11.7%; and Q4, LV-GLS worse than –9.2%.

Furthermore, unlike previous reports, the current study also demonstrated that LV-GLS, a highly sensitive imaging marker, can provide incremental prognostic value in a large group of patients with TS, in addition to LVEF. Using spline analysis, we also established thresholds of baseline LVEF and LV-GLS, below which the long-term outcomes were significantly worse. A small previous report demonstrated lack of improvement in GLS from baseline to follow-up in patients with TS; however, it did not report long-term outcomes.[17] An important point that needs to be recognized is that different strain software programs can derive different values for "normal"

Table 3. Univariate and Multivariate Competing Risk Analysis for Secondary Events (Deaths Excluding Documented Noncardiac Deaths)

Variable	Univariate		Multivariate	
	sHR (95% CI)	*P* Value	sHR (95% CI)	*P* Value
Age (for 10-y increase)	1.24 (1.10–1.39)	<0.001	1.18 (1.07–1.42)	<0.001
Male sex	1.58 (1.14–2.17)	0.012	1.39 (1.03–2.24)	0.038
Hypertension	1.29 (0.84–2.27)	0.348		
Hyperlipidemia	1.06 (0.73–1.52)	0.678		
Diabetes mellitus	1.29 (0.94–1.83)	0.183		
Triggers				
Unknown (reference)				
Emotional	1.08 (0.47–2.32)	0.782	1.05 (0.41–2.54)	0.845
Physical	1.64 (1.12–3.94)	0.012	1.47 (1.06–373)	0.032
Neurologic	1.68 (1.14–4.12)	0.014	1.52 (1.05–3.49)	0.024
β-Blockers	0.68 [0.48–0.91]	0.011	0.71 (0.51–0.97)	0.037
ACEI	0.87 (0.42–2.12)	0.392		
Statins	0.83 (0.32–2.03)	0.309		
Aspirin	0.63 (0.39–0.88)	0.011	0.68 (0.41–0.95)	0.031
Peak troponin I at presentation	1.39 [1.20–1.58]	<0.001	1.27 (1.10–1.38)	<0.001
Baseline LVEF (continuous variable)*	1.03 (1.01–1.04)	<0.001	1.02 (1.01–1.04)	0.0289
Worse baseline LV-GLS (continuous variable)†	1.08 (1.03–1.17)	0.003	1.04 (1.01–1.11)	0.034
Apical ballooning	1.21 [0.65–1.87)	0.842		
Baseline RVSP	1.24 (1.10–1.52)	<0.001	1.10 (0.91–1.32)	0.192
Cardiogenic shock at initial presentation	2.35 (1.48–2.68)	<0.001	2.12 (1.28–2.83)	<0.001

Because long-term cardiac and noncardiac deaths were competing risks, univariate and multivariate survival analyses were also performed using the competing risk regression analysis (Fine–Gray proportional subhazards model), and sHRs were calculated. ACE indicates angiotensin converting enzyme; ARB, angiotensin receptor blockers; LVEF, left ventricular ejection fraction; LV-GLS, left ventricular global longitudinal strain; RVSP, right ventricular systolic pressure; and sHR, subdistribution hazard ratio.

*Findings were similar if LVEF was used as a categorical variable at a cutoff of 35%.

†The interaction term between LVEF and LV-GLS was significant. The findings were similar if LV-GLS (continuous variable) was substituted for LVEF (continuous variable) in multivariate analysis.

cutoffs. However, it has also been previously demonstrated that LV-GLS values obtained using velocity vector imaging software (similar to our study) were similar for different echocardiography vendors.[25] It is possible that the outcomes of patients with TS are related to their ability to recover their LV function.

Although the mechanism behind the development of TS remains elusive and controversial, it is thought to be due to exaggerated sympathetic stimulation.[3] Another potential theory suggests that apical ballooning and TS are the result of severe, sustained spasm of many or all coronary vessels caused by potential endothelial dysfunction.[26] A potential role for acetylcholine testing was suggested to identify patients who would be at an increased risk of recurrent TS and likely have worse long-term outcomes. However, these findings require large-scale prospective validation.

Clinical Implications

Based on the results of this study and the previous report, identifying the trigger for TS might be crucial to potentially gauging long-term survival. In addition, relying on LVEF as a sole marker of cardiac functional improvement may not be an optimal strategy; we might need more sensitive markers like LV-GLS to further risk stratify. Whether there is a difference in temporal trend of LVEF versus LV-GLS improvement during follow-up (and its clinical or prognostic value) remains to be studied. Moreover, with increasing utilization of novel biomarkers and cardiac magnetic resonance in the diagnostic algorithm of TS, newer potential prognostic markers could be developed. Finally, instituting appropriate long-term medical therapy and closer follow-up is crucial to ensure improved long-term survival. Nevertheless, these data are hypothesis generating and require multicenter, potentially prospective validation.

Limitations

This retrospective observational study had potential for selection bias. There was a higher prevalence of cardiogenic shock in our study sample, likely because of tertiary referral bias. Also in the current

study, data on recurrence of TS were not available based on clinical documentation. Individual patient management, including initiation of appropriate medical therapy, was left at the discretion of the evaluating and treating physicians. LV-GLS measurements were performed on stored echocardiographic images, and the data were not available to the treating physicians. Furthermore, cardiac magnetic resonance was not uniformly performed in all patients; consequently, these data were not formally analyzed. Our primary outcome was all-cause mortality; however, the findings were similar even in secondary outcomes analysis.

CONCLUSIONS

In the current large single-center study of patients with TS, we demonstrated that patients with documented neurologic or physical triggers had significantly worse survival than those with emotional or undetermined triggers. In addition, baseline LVEF and LV-GLS provided incremental prognostic value for long-term mortality. Relying on LVEF as a sole marker of cardiac functional improvement may not be the optimal strategy, and we might need more sensitive markers like LV-GLS to further risk stratify. Whether there is a difference in temporal trend of LVEF versus LV-GLS improvement during follow-up (and its clinical or prognostic value) remains to be studied. These data are hypothesis generating and require multicenter, potentially prospective validation.

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