JACC: HEART FAILURE VOL. ■, NO. ■, 2018
© 2018 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER

Long-Term Prognosis and Outcome Predictors in Takotsubo Syndrome

A Systematic Review and Meta-Regression Study

Francesco Pelliccia, MD, PhD,[a] Vincenzo Pasceri, MD, PhD,[b] Giuseppe Patti, MD, PhD,[c] Gaetano Tanzilli, MD,[a] Giulio Speciale, MD,[b] Carlo Gaudio, MD,[a] Paolo G. Camici, MD[d]

ABSTRACT

OBJECTIVES This study assessed the incidence of long-term adverse outcomes in patients with Takotsubo syndrome (TTS).

BACKGROUND The long-term prognosis of TTS is controversial. It is also unclear whether presenting characteristics are associated with the subsequent long-term prognosis.

METHODS We searched the PubMed, Embase, and Cochrane databases and reviewed cited references up to March 31, 2018 to identify studies with >6 months of follow-up data.

RESULTS Overall, we selected 54 studies that included a total of 4,679 patients (4,077 women and 602 men). Death during admission occurred in 112 patients (2.4%), yielding a frequency of 1.8% (95% confidence interval [CI]: 1.2% to 2.5%), with significant heterogeneity ($I^2 = 78\%$; $p < 0.001$). During a median follow-up of 28 months (interquartile range: 23 to 34 months), 464 of 4,567 patients who the survived index admission died (103 because of cardiac causes and 351 because of noncardiac issues). The annual rate of total mortality was 3.5% (95% CI: 2.6% to 4.5%), with significant heterogeneity ($I^2 = 74\%$; $p < 0.001$). Overall, 104 cases of recurrence of TTS were detected during follow-up, yielding a 1.0% annual rate of recurrence (95% CI: 0.7% to 1.3%), without significant heterogeneity ($I^2 = 39\%$; $p = 0.898$). Meta-regression analysis showed that long-term total mortality in each study was significantly associated with older age ($p = 0.05$), physical stressor ($p = 0.0001$), and the atypical ballooning form of TTS ($p = 0.009$).

CONCLUSIONS Our update analysis of patients discharged alive after TTS showed that long-term rates of overall mortality and recurrence were not trivial, and that some presenting features (older age, physical stressor, and atypical ballooning) were significantly associated with an unfavorable long-term prognosis. (J Am Coll Cardiol HF 2018;■:■–■)

Takotsubo syndrome (TTS) is becoming routinely recognized and is now considered a frequent cause of acute heart failure in the real world (1-3). Despite recent progress in understanding of its pathophysiology and clinical correlates (1), the long-term outcome of the condition remains controversial. Prognosis of patients with TTS has long been said to be associated with a favorable outcome after the acute phase, with full recovery of left ventricular function and a mortality similar to healthy subjects (4,5). However, recent studies, have challenged the notion that TTS portends a benign outcome (6,7), stating that long-term mortality is higher compared with mortality in the general population (8), and outcomes resemble those of patients with acute coronary syndrome (9) and ST-elevation myocardial infarction (10). Along with the current uncertainty about the natural history of TTS, it remains unclear whether presenting characteristics in the acute phase are associated with the subsequent long-term prognosis.

We performed an updated systematic review and meta-regression analysis of studies that included patients with TTS that have been published since its original description to: 1) estimate the long-term

From [a]Department of Cardiovascular Sciences, La Sapienza University, Rome, Italy; [b]Interventional Cardiology Unit, San Filippo Neri Hospital, Rome, Italy; [c]Department of Cardiology, University of L'Aquila, L'Aquila, Italy; and the [d]Department of Cardiology, Vita e Salute University and San Raffaele Hospital, Milan, Italy. Dr. Camici has been a consultant for Servier. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received August 6, 2018; revised manuscript received October 7, 2018, accepted October 8, 2018.

ISSN 2213-1779/$36.00 https://doi.org/10.1016/j.jchf.2018.10.009

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

STROBE = Strengthening of Reporting of Observational Studies in Epidemiology

TTS = Takotsubo syndrome

annual rate of total mortality and recurrence after the index episode; and 2) assess which clinical characteristics in the acute phase are associated with long-term outcome of discharged patients.

METHODS

This systematic review was conducted following current guidelines, including the Cochrane Collaboration and Meta-analysis of Observational Studies in Epidemiology (11) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocols (12). The review protocol was registered at the PROSPERO international prospective register of systematic reviews (Centre for Reviews and Dissemination, University of York, York, United Kingdom; CRD42018090167).

SEARCH STRATEGY. We searched the PubMed, Embase, and Cochrane databases up to March 31, 2018. Search keywords were "apical ballooning syndrome," "broken heart syndrome," "stress cardiomyopathy," "Takotsubo syndrome," and "Takotsubo cardiomyopathy." A thorough search through the bibliography of published trials, meta-analyses, and reviews was also performed, including studies presented or published in other languages. In addition, we searched the presentations at major cardiovascular scientific sessions, including meetings of the American College of Cardiology, American Heart Association, and European Society of Cardiology.

INCLUSION AND EXCLUSION CRITERIA. Studies were selected according to the following pre-specified inclusion criteria (all had to be met for inclusion): 1) diagnosis of TTS on the basis of the Mayo Clinic criteria (13); 2) selection of the most recent publication when a patient population was reported on in separate publications; and 3) a comprehensive reporting of long-term outcomes after the index episode of TTS. All studies had to report results with a follow-up duration of ≥6 months. Exclusion criteria included duplicate reporting, in which case the article that reported the largest sample of patients with TTS was selected, or if the number of patients were equal, the study with the largest number of overall patients was selected. To avoid possible overlap between cohorts, multicenter international registries were excluded. Single case reports and previous systematic reviews on TTS were also excluded.

STUDY SELECTION. Retrieved citations were first screened independently by 2 unblinded investigators (F.P. and V.P.). Studies identified as potentially relevant on the basis of title or abstract were selected for full review. The reviewers independently assessed these investigations for eligibility based on the previously mentioned inclusion and exclusion criteria. Disagreement was resolved by consensus with third party adjudication. After excluding duplicates, studies were screened to identify potentially suitable articles that could be assessed for eligibility as full text.

OUTCOME MEASURES. Clinical outcomes analyzed were: 1) overall in-hospital mortality; 2) long-term mortality (i.e., total mortality, cardiac, and noncardiac deaths); and 3) overall incidence of recurrence of TTS during follow-up. Absolute numbers were recalculated when percentages were reported. Data were extracted onto standard spreadsheets and included date of study publication, years of enrollment, duration of follow-up, demographic characteristics, clinical characteristics at admission, and clinical outcomes, as previously defined. Methodological study quality was assessed using the Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) checklist of 22 items (14).

STATISTICAL ANALYSIS. Continuous variables were reported as mean ± SD, whereas skewed data were described as median (interquartile range). Statistical analyses were performed with R software 3.4.0 (The R Foundation for Statistical Computing, Vienna, Austria) using the Metafor Package (15). We tested heterogeneity of the included studies with Q statistics and the extent of inconsistency between results with I^2 statistics (significant heterogeneity was considered present for p values <0.10 and/or an I^2 >50%) (16). Random effects meta-regression analysis was performed to measure the impact of baseline characteristics on the effect size for pre-specified outcomes (in-hospital mortality, long-term total mortality, and recurrence during follow-up) (17). We used a random effects method because it did not assume that a true effect was common to all studies. Sensitivity analysis included a leave-one-out analysis to assess whether the pooled results were influenced by a single investigation. We also performed several subgroup analyses that included only investigations with large (n≥100) or small (n≤100) sample sizes, studies that enrolled patients from Asia, studies that reported an average follow-up of <5 years or those with a mean follow-up of <5 years, studies published in the past 5 years (2013 to 2018), or studies published >5 years ago (2012 or earlier). Presence of publication bias was estimated by the Rucker test (with arcsine transformation), which is best suited for binary outcomes (18) and funnel plot graph. Statistical significance was set at $p < 0.05$ (2-tailed).

RESULTS

The process of study selection (Online Figure 1) allowed identification of 54 studies for the meta-analysis (references listed in Online Table 1). Selected studies were published between 2006 and 2017 and included series of patients from North America, Europe, Asia, and Australia. All the study designs were observational. Quality assessment by the STROBE checklist disclosed a moderate quality in 21 studies and a high quality in 33 studies. Sample size in each study ranged from 6 to 505 participants. A total of 4,679 patients were included in the systematic review (**Table 1**). They were 602 men (13%) and 4,077 women (87%). The mean ages of the study populations ranged from 53 to 75 years.

PRESENTING FEATURES. Preceding events and clinical characteristics at referral could be evaluated in most studies (data detailed in Online Tables 2 and 3). In 36% of patients, onset of TTS was preceded by emotional stress; similarly, a physical stressor was identified in 36% of patients. Presenting symptoms included chest pain in nearly 64% of cases. Symptoms and/or signs of acute heart failure occurred in approximately one-half of all cases, because dyspnea was seen in 26% of patients and shock was present in 19% of patients at onset of TTS. Markers of myocardial injury were above the upper limits of normal in all studies. Moderate functional dysfunction was present in most patients, with a mean left ventricular ejection fraction ranging from 28% to 54% (mean: 40%; 95% confidence interval [CI]: 38% to 42%). An ST-segment elevation was evident in 44% of patients, whereas ST-segment downsloping was seen in 15% patients. Malignant ventricular arrhythmias were recorded in 10% of cases. The typical form of TTS characterized by apical ballooning was found in 72% of patients, whereas the atypical forms were shown in 28% of cases. Cardiovascular risk factors were assessed in several studies. Hypertension, dyslipidemia, diabetes mellitus, and smoking were detected in 59%, 34%, 14%, and 23% of TTS patients, respectively. Also, a few studies reported the prevalence of comorbidities (i.e., pulmonary [14%], endocrinological [10%], neurological [15%], and psychological diseases [18%]), as well as malignancy (17%). Most patients were discharged on angiotensin-converting enzyme inhibitor/angiotensin receptor blockers (92%) and beta receptor blockers (54%).

MAIN CLINICAL OUTCOMES. Death during the index admission occurred in 112 patients (2.4%) (**Table 1**), yielding a frequency of 1.8% (95% CI: 1.2% to 2.5%) (**Figure 1**), with significant heterogeneity ($I^2 = 78\%$; $p < 0.001$). All the studies assessed the post-discharge outcome of TTS patients for a minimum of 6 months. Follow-up ranged from 6 to 99 months (median: 28 months; interquartile range: 23 to 34 months). A total of 464 of 4,567 patients who the survived index admission died (10.2%). Of these, 103 patients died because of cardiac causes and 351 died because of noncardiac issues (**Table 1**). Annual rate of long-term total mortality was 3.5% (95% CI: 2.6% to 4.5%) (**Figure 2**), with significant heterogeneity ($I^2 = 74\%$; $p < 0.001$). The frequency of recurrence during follow-up was reported by 51 studies. Overall, 104 cases of recurrence of TTS were detected in the data set of 3,798 patients (**Table 1**). The adjusted annual incidence of recurrence of TTS was 1.0% (95% CI: 0.7% to 1.3%), without significant heterogeneity ($I^2 = 39\%$; $p = 0.898$) (**Figure 3**). Duration of follow-up did not influence yearly rates of mortality and recurrence that were 3.6% and 1,0%, respectively, in trials with an average length of follow-up of <5 years, and 2.7% and 0.7%, respectively, in trials with an average length of follow-up of >5 years. Also, no significant differences were found among studies performed in Europe, America, and Australia, and those carried out in Asia in in-hospital mortality (1.5% vs. 2.2%), long-term mortality (3.5% vs. 2.7%), and recurrence (0.9% vs. 2.1%).

META-REGRESSION

Meta-regressions of the effects of predisposing factors and clinical characteristics at presentation on subsequent outcomes showed discordant findings (Online Table 4). Univariate meta-regression analysis showed a significant association between in-hospital mortality and a physical stressor preceding the onset of TTS ($p = 0.003$; coefficient: 0.001; 95% CI: 0.000 to 0.001). Meta-regression showed that long-term total mortality in each study was significantly associated with older age ($p = 0.05$; coefficient: 0.002; 95% CI: 0.000 to 0.004), physical stressor ($p = 0.0001$; coefficient: 0.001; 95% CI: 0.000 to 0.002), and an atypical ballooning form ($p = 0.009$; coefficient: 0.001; 95% CI: 0.000 to −0.001) (**Figure 4**), but was not associated with acute heart failure at presentation (dyspnea: coefficient: 0.000; 95% CI: 0.000 to 0.001; $p = 0.56$; shock: coefficient: 0.000; 95% CI: −0.001 to 0.002; $p = 0.92$) (Online Table 4). Conversely, meta-regression analysis failed to reveal any significant relationship between presenting features and the subsequent recurrence of TTS.

TABLE 1 Rates of In-Hospital Mortality, Long-Term Outcome, and Recurrences in the Overall Population

First Author	Citation	Country	N	Females	Mean Age (Years)	In-Hospital Deaths	Mean Follow-Up (Months)	Total Deaths	Cardiac Deaths	Annual Rate of Mortality (%/Year)	Recurrence	Annual Rate of Recurrence (%/Year)
Kim JI	Cardiovasc Revasc Med 2018;19:247-50	USA	90	78	73	0	12	0	0	0	0	0
Abanador-Kamper N	BMC CardiovascDisord 2017;17:225	Germany	72	67	68	1	24	3	0	2.1	1	0.7
Sun T	Int J Cardiol 2017;244:7-12	Minnesota, USA	205	195	70	0	24	28	12	6.8	6	1.5
Weidner KJ	Ther Clin Risk Manag 2017;13:863-9	Germany	114	93	67	9	51	31	–	6.4	0	0
Matabuena Gomez-Limon J	Int J Cardiol 2017;228:97-102	Spain	66	64	67	0	44	4	2	1.7	5	2.1
Yayehd K	Arch Cardiovasc Dis 2016;109:4-12	France	117	107	71	0	12	3	1	2.6	0	0
Glaveckaitè S	Hellenic J Cardiol 2016;57:428-34	Lithuania	64	52	63	5	34	6	–	3.3	1	0.5
Girardey M	Circ J 2016;b80:2192-8	France	154	119	67	25	12	16	–	10.4	0	0
Vriz O	J Community Hosp Intern Med Perspect 2016;6:31082	Italy	55	48	68	3	69	5	0	1.6	6	1.0
Zalewska-Adamiec M	Neth Heart J 2016;24:511-9	Poland	101	90	67	3	30	16	0	6.3	0	0
Tornvall P	J Am Coll Cardiol 2016;67:1931-6	Sweden	505	442	67	0	60	35	15	1.4	–	–
Stiermaier T	Eur J HeartFail 2016;18:650-6	Germany	286	256	71	15	45	67	23	6.2	–	–
Auzel O	Am J Cardiol 2016;117:1242-7	France	90	87	72	2	36	14	–	5.2	–	–
Santoro F	Am J Emerg Med 2016;34:548-52	Italy	108	8	73	0	14	10	–	7.9	5	3.8
Khalighi K	J Cardiovasc Dis 2016;2:273-81	Pennsylvania, USA	12	12	66	0	99	1	0	1.0	4	4.1
Vizzardi E	J Cardiovasc Med 2015;16:326-30	Italy	42	42	67	0	12	1	0	2.4	0	0
Gopalakrishnan M	Am J Cardiol 2015;116:1586-90	Illinois, USA	56	45	65	5	28	10	–	7.7	1	0.8
Kuběna P	VnitrLek 2015;61:619-25	Czech Republic	47	42	62	0	12	0	0	0	1	2.1
Sharkey SW	Am J Cardiol 2015;116:765-72	Minnesota, USA	249	234	68	8	56	60	0	5.2	11	0.9
Nishida J	Heart Vessels 2015;30:789-97	Japan	251	184	70	1	31	10	10	1.5	7	3.8
Ribeiro	Arq Bras Cardiol 2014;102:80-5	Portugal	37	35	63	0	15	1	0	2.2	0	0
Showkathali	Eur J Intern Med 2014;25:132	United Kingdom	17	17	69	0	22	0	0	0	0	0
Bennett J	Acta Cardiol 2014;69:496-502	Belgium	139	123	67	10	12	7	3	5.0	6	4.2
Réglat C	Ann Cardiol Angeiol (Paris) 2014;63:75-82	France	70	63	69	0	57	7	1	2.1	1	0.3
Chan C	NZ Med J 2014;127:15-22	New Zealand	21	21	68	0	12	0	0	0	0	0
Patel	J Card Fail 2013;19:306-10	Pennsylvania, USA	224	212	69	2	16	54	11	18.1	7	2.4
Pullara A	Minerva Med 2013;104:537-44	Italy	26	22	71	2	12	0	0	0	2	7.7
Weihs V	Eur Heart J Acute Cardiovasc Care 2013;2:137-46	Austria	179	168	69	1	6	13	3	14.5	4	4.4
Nunez-Gil IJ	Rev Esp Cardiol 2012;65:996-1002	Spain	100	89	68	0	46	6	3	1.6	4	1.1
Samardhi H	Intern Med 2012;42:35-42	Australia	52	51	64	0	42	0	0	0	0	0
Cacciotti L	BMJ Open 2012;2:e001165	Italy	75	72	72	0	26	2	2	1.2	1	0.6
Brenner R	Clin Cardiol 2012;35:340-7	Switzerland	17	17	66	0	77	1	1	0.9	2	1.8
Pawlak M	Kardiol Pol 2012;70:233-40	Poland	41	39	69	0	33	1	–	0.9	1	0.9
Looi JL	Heart Lung Circ 2012;21:143-9	New Zealand	100	95	65	1	36	4	0	1.3	7	2.3
Buja P	J Cardiovasc Med 2012;13:790-4	Italy	54	47	72	2	19	6	3	7.0	2	2.3
Maekawa Y	Intern Med 2012;51:257-62	Japan	46	43	71	0	37	1	1	0.7	4	2,8
Chopard R	Arch Cardiovasc Dis 2011;104:509-17	France	87	52	53	0	12	0	0	0	0	0
Parodi	Chest 2011;139:887-92	Italy	116	106	73	2	24	11	7	4.7	2	0.9
Previtali	Am J Cardiol 2011;107:120-5	Italy	128	125	67	1	13	1	0	0.7	0	0
Teh AW	Heart Lung Circ 2010;19:63-70	Australia	23	20	65	0	20	2	0	5.2	0	0
Song BG	Heart Lung 2010;39:188-95	Korea	87	64	64	8	42	12	2	3.9	0	0
Ionescu CN	Heart Lung Circ 2010;19:601-5	Connecticut, USA	27	26	68	0	27	4	2	6.6	2	3.4
Primetshofer D	Wien Klin Wochenschr 2010;122:37-44	Austria	31	28	75	0	6	3	0	19.4	1	6.4
Eshtehardi P	Int J Cardiol 2009; 135:370-5	Switzerland	41	35	65	0	23	0	0	0	2	2.6
Vidi V	Am J Cardiol 2009;104:578-2	Massachusetts, USA	34	32	66	2	9	3	0	11.2	2	7.9
Regnante	Am J Cardiol 2009; 103:1015-9	Rhode Island, USA	70	66	67	1	36	2	0	0.9	2	0.8
Von Korn H	Cardiology 2009;112:42-8	Germany	21	19	68	0	13	1	1	4.3	0	0

Continued on the next page

TABLE 1 Continued

First Author	Citation	Country	N	Females	Mean Age (Years)	In-Hospital Deaths	Mean Follow-Up (Months)	Total Deaths	Cardiac Deaths	Annual Rate of Mortality (%/Year)	Recurrence	Annual Rate of Recurrence (%/Year)
Bahlmann E	Int J Cardiol 2008;124:32-9	Germany	15	14	69	0	19	2	0	8.4	0	0
Traulle S	Presse Med 2008;37:1547-54	France	14	13	70	0	10	0	0	0	0	0
Spedicato L	J Cardiovasc Med 2008;9:916-21	Italy	29	25	64	0	23	0	0	0	2	3.6
Mitchell	Am J Cardiol 2007;100:296-301	Texas, USA	22	22	66	0	12	0	0	0	0	0
Kurowski V	Chest 2007;132:809-16	Germany	35	34	72	3	17	0	0	0	2	4.1
Cangella F	Cardiovasc Ultrasound 2007;16;36	Italy	6	6	57	0	41	0	0	0	0	0
El Mahmoud R	Ann Cardiol Angeiol (Paris) 2006;55:210-15	France	11	11	70	0	15	0	0	0	0	0

See the Online Table 1 for complete reference information.

In particular, acute heart failure at presentation was not associated with recurrence of TTS (Dyspnea: coefficient: 0.000; 95% CI: 0.000 to 0.001; p = 0.50; shock: coefficient: 0.000; 95% CI: −0.001 to 0.000; p = 0.75) (Online Table 4). Also, meta-regression analysis showed no relationship between follow-up duration and long-term mortality (p = 0.16) or recurrence (p = 0.84) (Online Table 4).

SENSITIVITY ANALYSIS. The leave-one-out analysis showed that the pooled results were not influenced by a single trial, not even the larger study by Tornvall et al. (7). In addition, excluding studies with large (n≥100) or small (n≤100) sample sizes, studies that enrolled patients from Asia, studies that reported an average follow-up of <5 years or those with a mean follow-up of <5 years, studies published in the past 5 years (2013 to 2018), or those published >5 years ago (2012 or earlier) did not change the results of the meta-analysis. Rucker's test did not suggest publication bias (p = 0.41 for long-term mortality). Funnel plot analysis showed no asymmetry that suggested a significant risk of publication bias, and that the long-term mortality did not depend on the size of the studies (Online Figure 2).

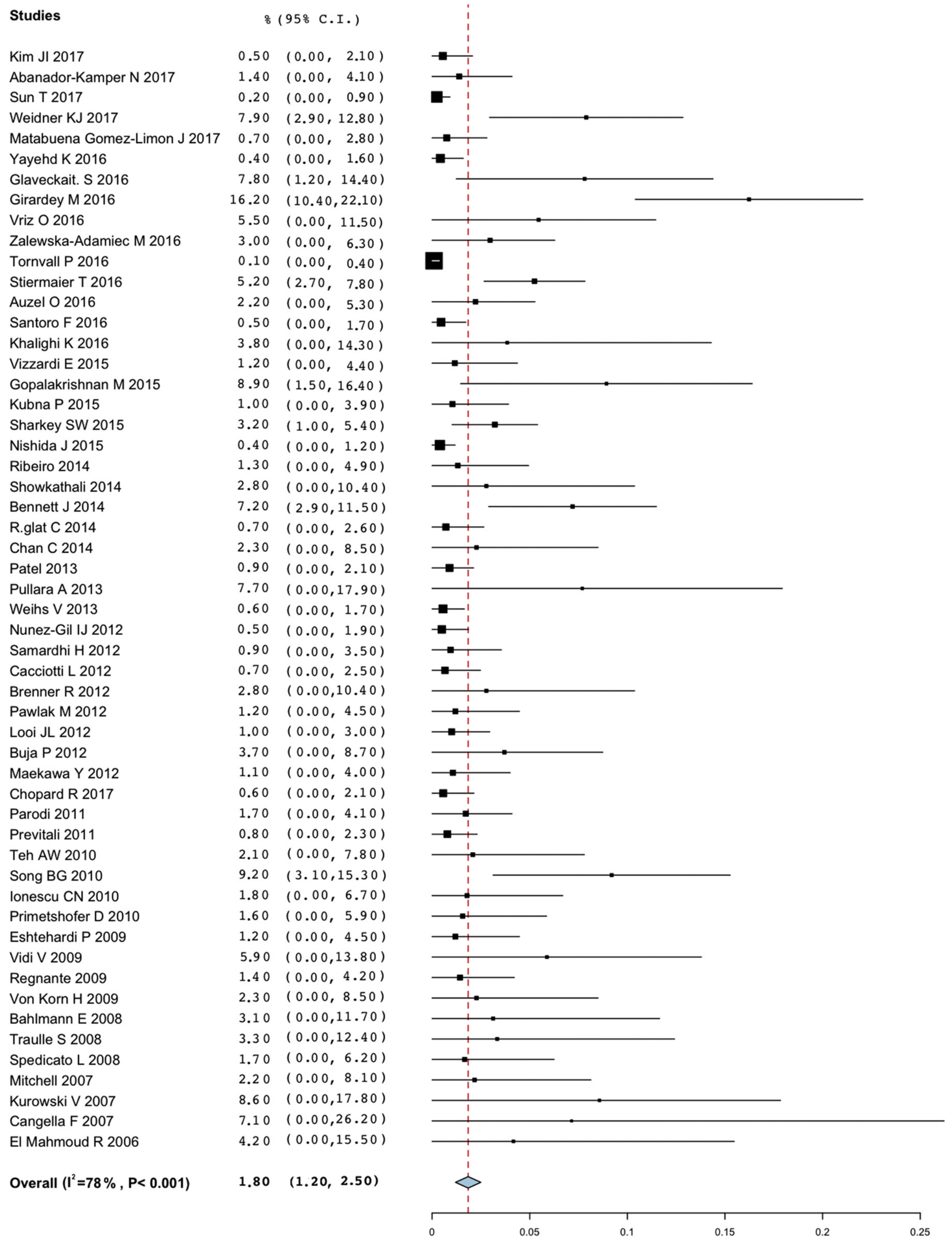
DISCUSSION

The present analysis provided long-term mortality data in the largest series of patients with TTS reported so far. Our systematic review of 54 investigations allowed description of the long-term, post-discharge outcomes of patients who experienced an episode of TTS in a large cohort of patients (n≥4,600) pooled from observational studies carried out in North America, Europe, Asia, and Australia. Specifically, we found that: 1) long-term rates of overall mortality and recurrence in patients discharged alive after TTS were not trivial; and 2) some presenting features (i.e., older age, physical stressor, and atypical ballooning) were significantly associated with an unfavorable long-term prognosis.

IN-HOSPITAL OUTCOME. TTS is commonly said to be a benign disease. Recently, a multicenter study that included only patients with TTS admitted to nonacademic hospitals recorded only a few cases of acute heart failure with no in-hospital deaths (19). In contrast, other studies that pooled data from referral centers showed that the rates of complications and in-hospital mortality might be similar to that of acute coronary syndromes (2,3). These observations highlighted the wide heterogeneity of TTS and were in keeping with the results of our investigation, because we found that the frequency of life-threatening complications (i.e., acute heart failure with shock [19%] and malignant arrhythmias [10%]) was relatively high, and in-hospital death occurred in 1.8% of cases. Of interest, with the exception of physical stressors, no significant association between any clinical characteristics at time of referral and in-hospital mortality was disclosed by multiregression analysis.

LONG-TERM OUTCOME. Data on long-term prognosis of patients with TTS are controversial. Originally, survival of patients with TTS discharged alive after the index episode was said to be similar to the general population (8). However, 2 large collaborative investigations highlighted the fact that long-term mortality of TTS patients did not differ from patients with acute coronary syndromes (6,7). Templin et al. (6) observed a death rate of 5.6% per patient-year during the follow-up of 1,750 patients evaluated in 26 international centers. Similarly, Tornvall et al. (10) reviewed the Swedish Coronary Angiography and Angioplasty Register and found that mortality rates of TTS in Sweden were worse than in

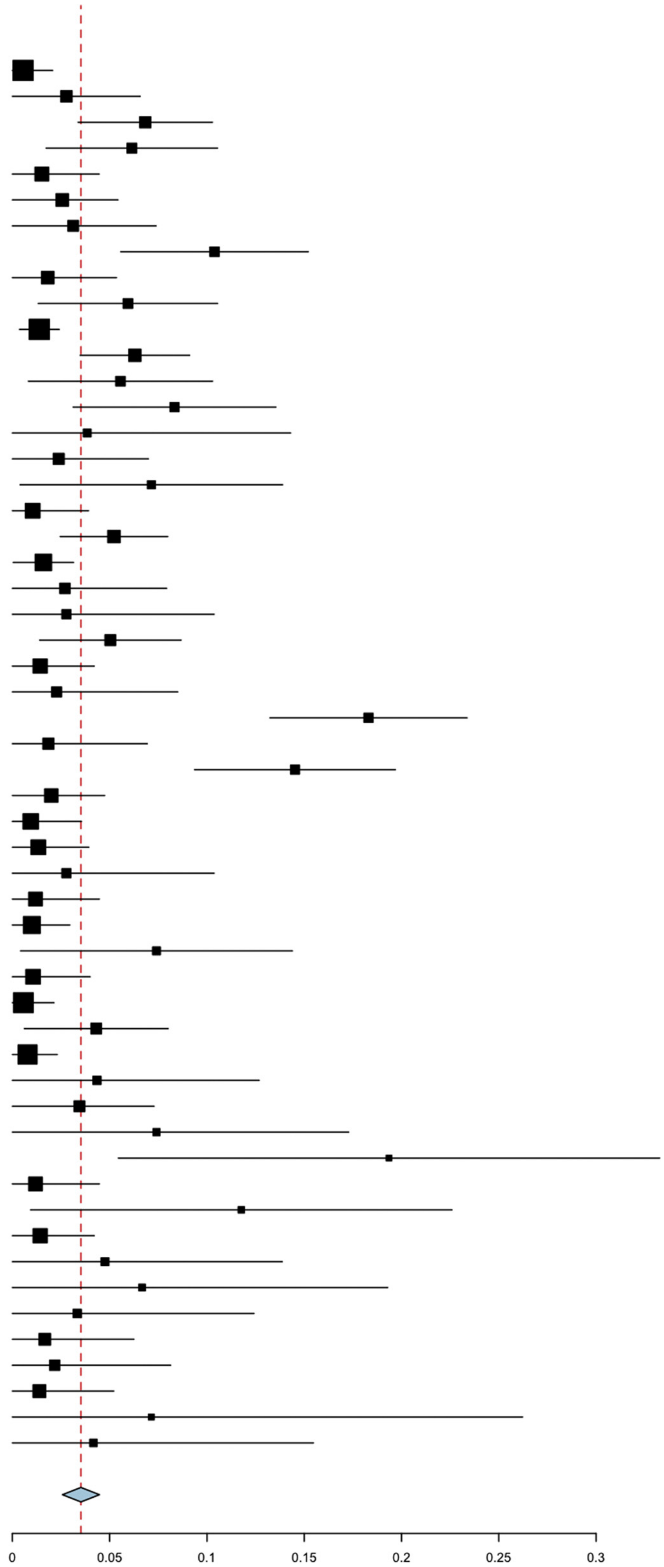
FIGURE 1 Individual and Overall Incidence for In-Hospital Mortality



Solid squares = weighted estimate of incidence for each single study. **Blue diamond** = overall estimated incidence. **Vertical line** = pooled averaged incidence estimate. **Horizontal bars** = 95% confidence intervals (C.I.s). References appear in Online Table 1.

FIGURE 2 **Individual and Overall Incidence for Annual Rate of Total Mortality**

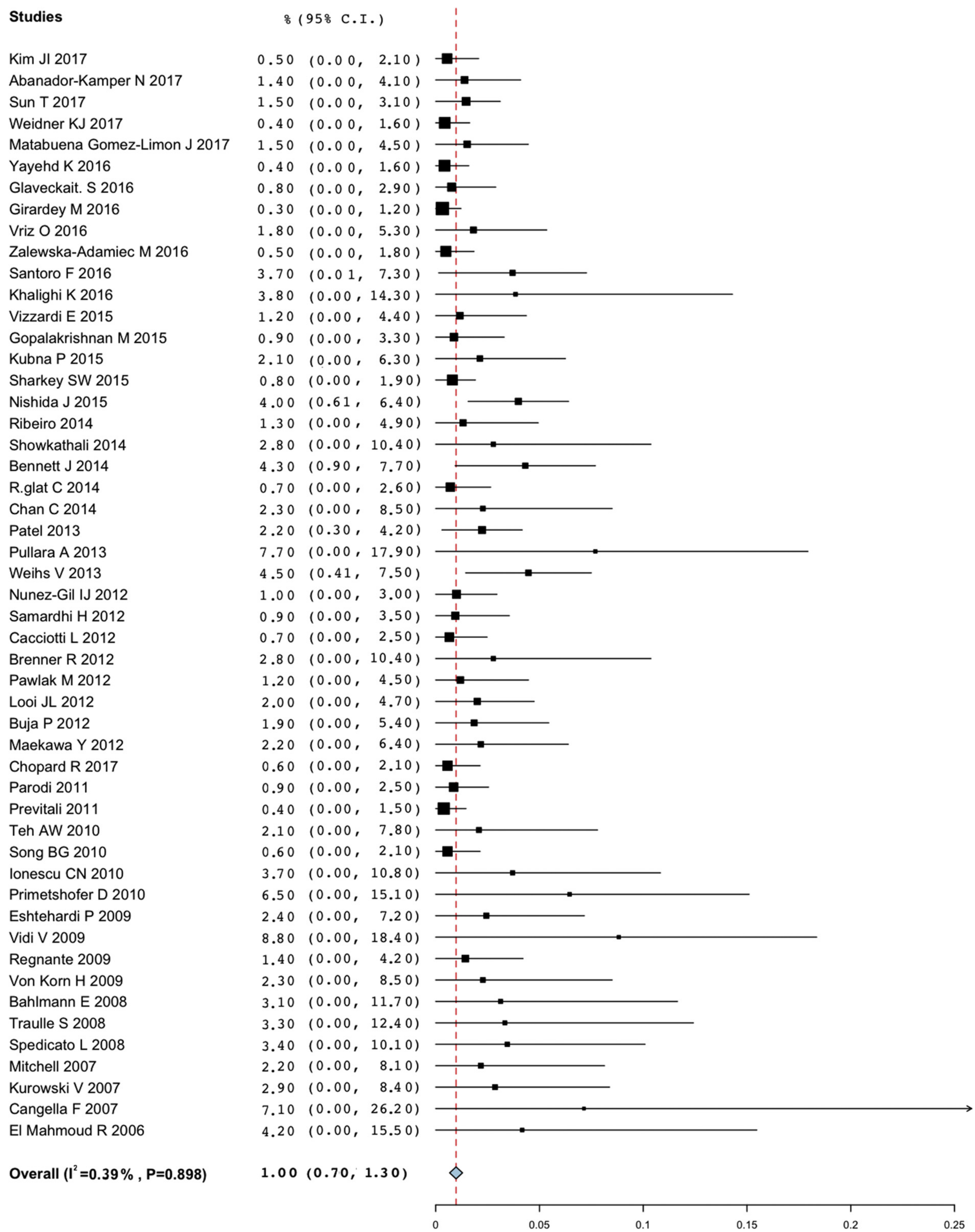
Studies	% (95% C.I.)
Kim JI 2017	0.50 (0.00, 2.10)
Abanador-Kamper N 2017	2.80 (0.00, 6.60)
Sun T 2017	6.80 (3.40, 10.30)
Weidner KJ 2017	6.10 (1.70, 10.50)
Matabuena Gomez-Limon J 2017	1.50 (0.00, 4.50)
Yayehd K 2016	2.60 (0.00, 5.40)
Glaveckait. S 2016	3.10 (0.00, 7.40)
Girardey M 2016	10.40 (5.60, 15.20)
Vriz O 2016	1.80 (0.00, 5.30)
Zalewska-Adamiec M 2016	5.90 (1.30, 10.60)
Tornvall P 2016	1.40 (0.40, 2.40)
Stiermaier T 2016	6.30 (3.50, 9.10)
Auzel O 2016	5.60 (0.80, 10.30)
Santoro F 2016	8.30 (3.10, 13.50)
Khalighi K 2016	3.80 (0.00, 14.30)
Vizzardi E 2015	2.40 (0.00, 7.00)
Gopalakrishnan M 2015	7.10 (0.40, 13.90)
Kubna P 2015	1.00 (0.00, 3.90)
Sharkey SW 2015	5.20 (2.50, 8.00)
Nishida J 2015	1.60 (0.00, 3.10)
Ribeiro 2014	2.70 (0.00, 7.90)
Showkathali 2014	2.80 (0.00, 10.40)
Bennett J 2014	5.00 (1.40, 8.70)
R.glat C 2014	1.40 (0.00, 4.20)
Chan C 2014	2.30 (0.00, 8.50)
Patel 2013	18.30 (1.32, 23.40)
Pullara A 2013	1.90 (0.00, 6.90)
Weihs V 2013	14.50 (0.94, 19.70)
Nunez-Gil IJ 2012	2.00 (0.00, 4.70)
Samardhi H 2012	0.90 (0.00, 3.50)
Cacciotti L 2012	1.30 (0.00, 3.90)
Brenner R 2012	2.80 (0.00, 10.40)
Pawlak M 2012	1.20 (0.00, 4.50)
Looi JL 2012	1.00 (0.00, 3.00)
Buja P 2012	7.40 (0.40, 14.40)
Maekawa Y 2012	1.10 (0.00, 4.00)
Chopard R 2017	0.60 (0.00, 2.10)
Parodi 2011	4.30 (0.60, 8.00)
Previtali 2011	0.80 (0.00, 2.30)
Teh AW 2010	4.30 (0.00, 12.70)
Song BG 2010	3.40 (0.00, 7.30)
Ionescu CN 2010	7.40 (0.00, 17.30)
Primetshofer D 2010	19.40 (5.40, 33.30)
Eshtehardi P 2009	1.20 (0.00, 4.50)
Vidi V 2009	11.80 (0.90, 22.60)
Regnante 2009	1.40 (0.00, 4.20)
Von Korn H 2009	4.80 (0.00, 13.90)
Bahlmann E 2008	6.70 (0.00, 19.30)
Traulle S 2008	3.30 (0.00, 12.40)
Spedicato L 2008	1.70 (0.00, 6.20)
Mitchell 2007	2.20 (0.00, 8.10)
Kurowski V 2007	1.40 (0.00, 5.20)
Cangella F 2007	7.10 (0.00, 26.20)
El Mahmoud R 2006	4.20 (0.00, 15.50)
Overall (I^2=74 %, P< 0.001)	**3.50 (2.60, 4.50)**



Solid squares = weighted estimate of incidence for each single study. **Blue diamond** = overall estimated incidence. **Vertical line** = pooled averaged incidence estimate. **Horizontal bars** = 95% confidence intervals (C.I.s). References appear in Online Table 1.

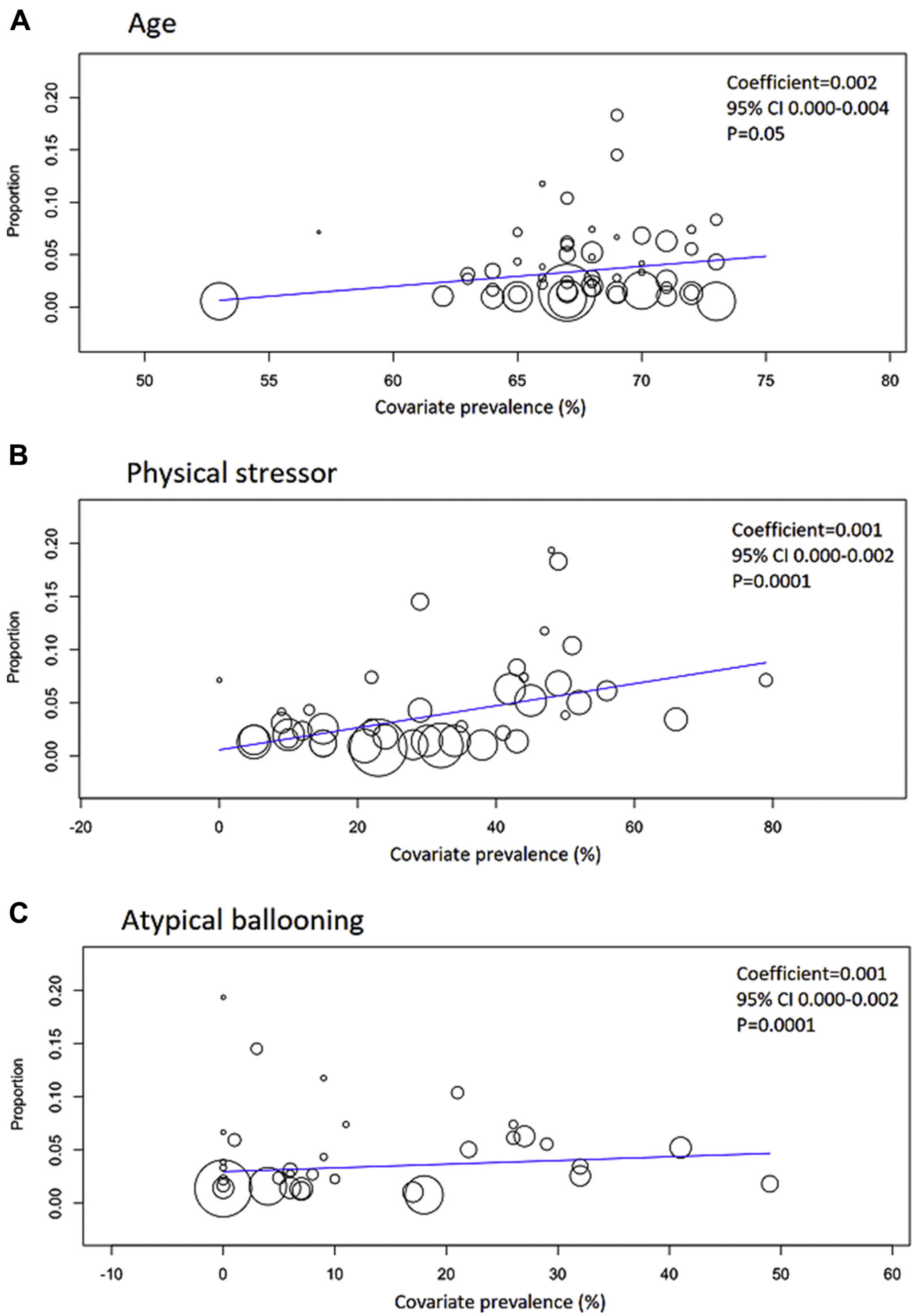
JACC: HEART FAILURE VOL. ■, NO. ■, 2018
■ 2018:■ - ■

FIGURE 3 Individual and Overall Incidence for Recurrence



Solid squares = weighted estimate of incidence for each single study. **Blue diamond** = overall estimated incidence. **Vertical line** = pooled averaged incidence estimate. **Horizontal bars** = 95% confidence intervals (C.I.s). References appear in Online Table 1.

FIGURE 4 **Meta-Regression Graphs**



Meta-regression graphs showing the association between long-term mortality and **(A)** age, **(B)** prevalence of physical stressors, and **(C)** frequency of atypical ballooning forms. Each **circle size** represents a study, telescoped by its weight in the analysis. The **x-axis** shows the prevalence of each covariate. The **y-axis** shows the incidence of long-term mortality. The regression line is calculated by the meta-regression model. References appear in Online Table 1. CI = confidence interval.

control subjects without ischemic heart disease and overlapped with those of patients with coronary artery disease. At variance with these observations, we found an annual rate of total mortality of 3.5% that was in keeping with a number of studies that reported that the long-term prognosis of TTS survivors was more benign than after an acute coronary syndrome (5,20). Of interest, most deaths (78%) were due to noncardiac causes, and only 22% of deaths were labeled as cardiac. Although a substantial contribution of cardiovascular mortality to the outcome in TTS was observed in some small series (8,21), our results were consistent with those studies that reported that late mortality after TTS was largely due to noncardiac causes (4,5), which suggested that concomitant conditions played a major long-term prognostic role. These observations were in line with the evidence that most cases of TTS occurred in patients with comorbidities, including neurological, psychiatric, pulmonary, kidney, liver, and connective tissue diseases (22), which are associated with endothelial dysfunction and might therefore constitute a major predisposing factor for TTS (23).

TTS RECURRENCE. Since original reports of the condition, recurrence has been noted to be an option in the clinical course of patients who experience a first episode of TTS (2,3). Interestingly, recurrent episodes are remarkably similar to the index TTS, demonstrating an ongoing propensity for the condition. In our series, the annual incidence of recurrence of TTS was 1.0%. This percentage was at variance to that of Sharkey et al. (5), who reported a recurrence rate of 5%, but is in keeping with the results of Singh et al. (24). These authors found that, among the 1,664 TTS patients included in a meta-analysis of 31 cohorts, the annual incidence of recurrence was roughly 1.5%. Regardless of its frequency, available observations underscore the importance of taking into consideration the small but real risk of TTS recurrence. Unfortunately, it remains unclear which factors might predict this complication. Singh et al. (24) stated that the recurrence rate was inversely correlated with prescription of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and that patients with severe TTS at index admission were noted to have more recurrences. However, our meta-regression was unable to disclose any significant association between presenting features or pharmacological treatment during follow-up and the risk of recurrence.

FACTORS ASSOCIATED WITH LONG-TERM OUTCOME. In our study, meta-regression analysis identified 3 factors (e.g., older age, physical stressors, and atypical ballooning pattern) to be significantly associated with long-term mortality. An increased risk of death in older patients was reported previously, in agreement with our findings (6). Our results are also in keeping with previous studies that demonstrated an increased risk of death in patients with TTS that was associated with secondary forms of TTS, which was usually triggered by a physical stressor compared with patients with primary TTS (e.g., generally preceded by an emotional event) (24,25). The major prognostic role of physical activities, medical conditions, or procedures were also recently outlined by Ghadri et al. (26) who reviewed the long-term mortality of 1,613 TTS patients included in the International Takotsubo registry. Results showed that TTS patients with physical stress had higher mortality rates than acute coronary syndrome patients during long-term follow-up, whereas patients with emotional stress had better outcomes compared with coronary artery disease patients (26). At variance with our results, outcomes of typical and atypical TTS were found to be comparable after adjustment for confounders (27). However, the possibility existed that forms of TTS that are not limited to the apical region were associated with a more extensive myocardial involvement (28). With regard to potential mechanisms that might affect the long-term prognosis of TTS patients, it was recently recognized that, despite apparent early recovery, contractile dysfunction might develop with time due to a process of cardiac inflammation, which could lead to global microscopic fibrosis, which could be detected as early as 4 months (29). On the basis of our results, we speculated that stronger triggers (e.g., physical stressor) that occurred in more vulnerable patients (e.g., older adults) might result in a larger extent of myocardial damage, which, in turn, could lead to global left ventricular stunning in the acute phase (e.g., atypical ballooning) and eventually to a worse outcome in the long term.

STUDY LIMITATIONS. Our study had the limitations intrinsic in any study-level meta-analysis. Duplicate reporting of data is a potential methodological limitation that was seriously considered. For this reason, multicenter international registries were excluded to avoid overlap between cohorts. Observational investigations might have selection biases, and systematic pooling of studies with different baseline characteristics of patients might affect results. Despite these limitations, we assessed the methodological quality of the included studies, with most resulting in high quality. In addition, observational studies deal with real-world populations, and therefore, can provide reliable scientific information. Treatment was empirical, so it was not possible to reliably assess the effects of the medication regimens on long-term outcomes. The lack of control groups, including either age- and sex-matched healthy subjects or patients with acute coronary syndrome, did not allow us to draw definite conclusions about differences in long-term outcomes between TTS patients and the general population or coronary artery disease patients. Meta-analysis showed that there was significant heterogeneity in presenting features and outcome among the studies. The studies selected for this meta-analysis differed in multiple aspects (i.e., baseline characteristics, sample size, length of follow-up, and so on). However, to evaluate the stability of the results, we performed a leave-one-out sensitivity analysis and were able to show that omission of each study did not change the overall results.

CONCLUSIONS

Our updated systematic review and meta-regression analysis of patients discharged alive after TTS showed that total mortality and recurrence occurred more frequently than commonly thought. Also, older age, physical stressors, and atypical ballooning forms were the most relevant factors associated with an unfavorable long-term prognosis.

ADDRESS FOR CORRESPONDENCE: Dr. Francesco Pelliccia, Department of Cardiovascular Sciences, Sapienza University, Viale del Policlinico 155, 00166 Rome, Italy. E-mail: f.pelliccia@mclink.it.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Patients with TTS are commonly believed to have a good long-term outcome after the index episode. Our updated analysis of patients discharged after TTS hospitalization showed that long-term rates of overall mortality and recurrence were not trivial. We were able to identify some presenting features (i.e., older age, physical stressor, and atypical ballooning) that are significantly associated with an unfavorable long-term prognosis.

TRANSLATIONAL OUTLOOK: The long-term outcome of patients with TTS should be prospectively investigated in appropriately designed and sized international, multicenter studies. Specifically, further studies are needed to test the hypothesis that stronger triggers (e.g., physical stressor) that occur in more vulnerable patients (e.g., older adults) might result in a larger extent of myocardial damage, which, in turn, could lead to global left ventricular stunning in the acute phase (e.g., atypical ballooning) and eventually to a worse outcome in the long term.

REFERENCES

1. Pelliccia F, Kaski JC, Crea F, Camici PG. Pathophysiology of takotsubo syndrome. Circulation 2017;135:2426–41.

2. Ghadri JR, Wittstein IS, Prasad A, et al. International expert consensus document on takotsubo syndrome (part I): clinical characteristics, diagnostic criteria, and pathophysiology. Eur Heart J 2018;39:2032–46.

3. Ghadri JR, Wittstein IS, Prasad A, et al. International expert consensus document on takotsubo syndrome (part II): diagnostic workup, outcome, and management. Eur Heart J 2018;39:204–62.

4. Elesber AA, Prasad A, Lennon RJ, Wright RS, Lerman A, Rihal CS. Four-year recurrence rate and prognosis of the apical ballooning syndrome. J Am Coll Cardiol 2007;50:448–52.

5. Sharkey SW, Windenburg DC, Lesser JR, et al. Natural history and expansive clinical profile of stress (tako-tsubo) cardiomyopathy. J Am Coll Cardiol 2010;55:333–41.

6. Templin C, Ghadri JR, Diekmann J, et al. Clinical features and outcomes of takotsubo (stress) cardiomyopathy. N Engl J Med 2015;373:929–38.

7. Tornvall P, Collste O, Ehrenborg E, et al. A case-control study of risk markers and mortality in takotsubo stress cardiomyopathy. J Am Coll Cardiol 2016;67:1931–6.

8. Parodi G, Bellandi B, Del Pace S, et al. Natural history of takotsubo cardiomyopathy. Chest 2011; 139:887–92.

9. Redfors B, Vedad R, Angerås O, et al. Mortality in takotsubo syndrome is similar to mortality in myocardial infarction. A report from the SWEDEHEART registry. Int J Cardiol 2015;185: 282–9.

10. Stiermaier T, Moeller C, Oehler K, et al. Long-term excess mortality in takotsubo cardiomyopathy: predictors, causes and clinical consequences. Eur J Heart Fail 2016;18:650–6.

11. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of reporting of meta-analyses. Lancet 1999;354: 1896–900.

12. Liberati A, Liberati A, Altman DG, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700.

13. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370:1453–7.

14. Prasad A, Lerman A, Rihal CS. Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction. Am Heart J 2008;155:408–17.

15. Viechtbauer W. Conducting meta-analyses in R with the meta for package. J Stat Software 2010; 36:1–48.

16. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21: 1539–58.

17. Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? Stat Med 2002;21:1559–73.

18. Rucker G, Schwarzer G, Carpenter J. Arcsine test for publication bias in meta-analysis with binary outcomes. Stat Med 2008;27:746–63.

19. Yayehd K, N'da NW, Belle L, et al. Management of takotsubo cardiomyopathy in non-academic hospitals in France: The Observational

French SyndromEs of TakoTsubo (OFSETT) study. Arch Cardiovasc Dis 2016;109:4–12.

20. Bybee KA, Prasad A, Barsness GW, et al. Clinical characteristics and thrombolysis in myocardial infarction frame counts in women with transient left ventricular apical ballooning syndrome. Am J Cardiol 2004;94:343–6.

21. Nunez-Gil IJ, Molina M, Bernardo E, et al. Takotsubo syndrome and heart failure: long-term follow-up. Rev Esp Cardiol 2012;65:996–1002.

22. Pelliccia F, Greco C, Vitale C, Rosano G, Gaudio C, Kaski JC. Takotsubo syndrome (stress cardiomyopathy): an intriguing clinical condition in search of its identity. Am J Med 2014;127:699–704.

23. Pelliccia F, Parodi G, Greco C, et al. Comorbidities frequency in takotsubo syndrome: an international collaborative systematic review including 1109 patients. Am J Med 2015;128:654.e11–9.

24. Singh K, Carson K, Usmani Z, et al. Systematic review and meta-analysis of incidence and correlates of recurrence of takotsubo cardiomyopathy. Int J Cardiol 2014;174:696–701.

25. Nunez-Gil IJ, Almendro-Delia M, Andres M, et al. Secondary forms of takotsubo cardiomyopathy: a whole different prognosis. Eur Heart J Acute Cardiovasc Care 2016;5:308–16.

26. Ghadri JR, Kato K, Cammann VL, et al. Long-term prognosis of patients with takotsubo syndrome. J Am Coll Cardiol 2018;72:874–82.

27. Ghadri JR, Cammann VL, Napp LC, et al. Differences in the clinical profile and outcomes of typical and atypical takotsubo syndrome: data from the International Takotsubo Registry. JAMA Cardiol 2016;1:335–40.

28. Eitel I, von Knobelsdorff-Brenkenhoff F, Bernhardt P, et al. Clinical characteristics and cardiovascular magnetic resonance findings in stress (takotsubo) cardiomyopathy. JAMA 2011;306:277–86.

29. Schwarz K, Ahearn T, Srinivasan J, et al. Alterations in cardiac deformation, timing of contraction and relaxation, and early myocardial fibrosis accompany the apparent recovery of acute stress-induced (takotsubo) cardiomyopathy: an end to the concept of transience. J Am Soc Echocardiogr 2017;30:745–55.

KEY WORDS long-term, outcome, prognosis, recurrence, Takotsubo syndrome

APPENDIX For supplemental Figures and tables, please see the online version of this paper.