Psychology, Health & Medicine

ISSN: 1354-8506 (Print) 1465-3966 (Online) Journal homepage: https://www.tandfonline.com/loi/cphm20

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To cite this article: E. Olliges, C. Burgdorf, K.H. Ladwig, C. Moeller, D. Deftu-Kloes, S. Pohl, B. Ruettner, G. Richardt, K. Meissner, A. Steger, L. Goetzmann & J. Ronel (2020): Psychosocial and physical long-term outcome in patients with a history of takotsubo cardiomyopathy or myocardial infarction - a multi-centered case control study, Psychology, Health & Medicine, DOI: 10.1080/13548506.2020.1722315

To link to this article: https://doi.org/10.1080/13548506.2020.1722315

Published online: 30 Jan 2020.

PSYCHOLOGY, HEALTH & MEDICINE
https://doi.org/10.1080/13548506.2020.1722315

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Psychosocial and physical long-term outcome in patients with a history of takotsubo cardiomyopathy or myocardial infarction - a multi-centered case control study

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ABSTRACT

Physical long-term impacts of Takotsubo Cardiomyopathy (TTC) remain controversial and an underestimation of their severity becomes increasingly evident. Even less is known about mental long-term impacts of TTC. This study aims at a better understanding of the physical and mental long-term effects of TTC in comparison to myocardial infarctions (MI).

On average 5 years after disease onset, 68 TTC patients and 68 age- and sex-matched MI patients were assessed for disease-related quality of life, depression, anxiety, chronic stress, social support, resilience, and life events prior to disease onset. Scores of TTC and MI patients were compared to each other and to normative references values. Regression analyses were used to evaluate the predictive value of the number of life events prior to disease onset for physical and mental long-term outcomes.

Both groups displayed higher scores in depression and anxiety, higher levels of chronic stress, and lower scores in physical and mental quality of life in comparison to norm samples, while social support did not differ from norms. No differences between the two patient groups were observed. Within both groups, the majority of patients (TTC: 69.1%; MI: 60.3%) reported stressful life events prior to disease onset. In TTCs and MIs, the number of events had a significant impact on long-term mental health and chronic stress. Notably, both patient collectives scored higher in resilience than healthy controls.

Results suggest negative long-term impacts of TTC on mental and physical wellbeing, comparable to those of MI. Besides a good

ARTICLE HISTORY

Received 3 May 2019
Accepted 25 December 2019

KEYWORDS

Takotsubo cardiomyopathy; myocardial infarction; disease outcome; anxiety; depression; stress; quality of life; resilience; coping strategies

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somatic-medical care, psychotherapeutic support, including the development of functional coping strategies, might be warranted for TTC patients. The long-term impact of TTC should be taken as serious as that of MI.

Introduction

The Takotsubo Cardiomyopathy (TTC; also termed 'Stress-induced cardiomyopathy', 'Broken- Heart Syndrome') is considered as rare, reversible, and acquired form of primary myocardial disorders. After its first description in Japan in 1990, TTC became increasingly acknowledged and gained worldwide recognition (Kurisu et al., 2002; Kurowski et al., 2007; Parodi et al., 2007; Sato, 1990). TTC is characterized by an acute functional disturbance in the contraction of the myocardium, primarily affecting mid and apical areas of the left ventricle. The modified shape of the left ventricle at the end of the systole (visualized by means of angiographic examinations) evokes the form of a Japanese octopus trap, termed 'Tako-Tsubo'. Data on the prevalence of TTC vary (Deshmukh et al., 2012; Maron et al., 2006). Approximately 0.07–3% of patients with suspected Acute Coronary Syndrome (ACS), are diagnosed with TTC after cardiac catheter examination. Nearly 90% of all TTC patients are postmenopausal women. Hormones (e.g. estrogen) seem to function as protection factors, but currently, it is unclear, why women are more prone to develop TTC (Grodstein and Stampfer, 1995). The clinical presentation of TTC and MI is often similar. Both patient groups are mostly reporting sudden chest pain and pronounced dyspnea, accompanied by electrocardiogram alterations, and an increase in cardiac biomarkers. Hence, TTC can only be distinguished from MI via heart catheter examination (Ghadri, Wittstein, et al., 2018; Klinceva et al., 2007; Kurowski et al., 2007; El Mahmoud et al., 2015; Parodi et al., 2007; Schofer et al., 2014; Wedekind, Möller, & Scholz, 2006). Coronary arteries are mostly unaffected in TTC patients. However, coronary artery disease (CAD) can simultaneously exist (Haghi et al., 2010; Templin et al., 2015).

From a psychophysiological perspective, an excessive activation of the sympathetic nervous system is discussed to be a major factor for the development of TTC and several studies suggest that elevated catecholamine concentrations function as mediating mechanism (Borchert et al., 2017; Wittstein, 2016; Frustaci et al., 1991, Khullar et al., 1989).. Nonetheless, the etiology of TTC remains unclear. Acute emotionally or physical stressful events prior to the onset of the disease could be identified in approximately 70% of TTC patients, whereas research on chronic stress in TTC remains limited (Delmas et al., 2013; Summers, Lennon, & Prasad, 2010; Templin et al., 2015).

Based on the observation of a rapid normalization of the systolic left-ventricular ejection fraction (LVEF) and regional wall motion after the acute phase, TTC is usually considered a benign, reversible disorder (Elesber et al., 2007; Pilgrim & Wyss, 2008; Schneider et al., 2010). However, data on long-term follow-ups are sparse and ambivalent (Khalighi, Farooq, Aung, & Oo, 2015). Whilst survival rates have been found not to differ from those of an age- and sex-matched population (Elesber et al., 2007; Ghadri, Kato et al., 2018, Ghadri, Wittstein et al., 2018; Valbusa et al., 2008), several studies described similar early and late mortality in TTC patients compared to patients after MI and

a significantly higher mortality rate in comparison with a control group of the same age and sex (Ghadri, Kato et al., 2018; Redfors et al., 2015; Sobue et al., 2017; Templin et al., 2015). Apart from cardiovascular events, this appears to be due to an increased prevalence of non-cardiac comorbidities, especially cancer (Burgdorf, Kurowski, Bonnemeier, Schunkert, & Radke, 2008; Burgdorf, Nef, Haghi, Kurowski, & Radke, 2010; Sharkey et al., 2010; Singh et al., 2014). Furthermore, recent studies indicate that TTC may have long-lasting negative cardiac consequences in terms of persistent heart failure symptoms, worse than previously reported (Ionescu, Aguilar-Lopez, Sakr, Ghantous, & Donohue, 2010; Scally et al., 2018).

First studies examined the question of whether the type of trigger (e.g. emotional or physical) is associated with short term disease outcome. Again, results represent a high variability. Higher age and the occurrence of emotional (e.g. workplace problems or loss of a relative) seem to predict more favorable outcomes, instead of physical events (e.g. infections or surgeries) (Templin et al., 2015). Further, sex appears to play a crucial role; negative endpoints, such as in-hospital death occurred more often among men (Sobue et al., 2017; Templin et al., 2015). Compare et al., however, reported that type of trigger made no differences in quality of life (QoL) and emotional burden one year after disease onset (Compare et al., 2014).

Contrary to the field of cardiovascular disease (CVD), research on risk and protection factors as well comorbidities in TTC patients is less advanced (Freedland, 2017; Freedland et al., 2003; Ladwig et al., 2017, 2013). Psychosocial risk factors, for instance stressful life events (e.g. loss of a relative or financial stress) and especially chronic stress, as well as anxiety and depression are highly associated with an increased risk for the development of CVD and an unfavorable disease progression (Dimsdale, 2008; Miller et al., 2002; Mostofsky et al., 2012; Penninx, 2017; Rosengren et al., 2004). Simultaneously, social support and resilience, as the individual's salutogenic ability to functionally respond to, and integrate specific negative conditions or life crises, have emerged to serve as protection factors (Barth, Schneider, & Von Känel, 2010). First studies also indicate higher levels of depressive and anxiety symptoms as well as increased distress in patients with a history of TTC (Compare et al., 2014; Mudd, Kapur, Champion, Schulman, & Wittstein, 2007; Nguyen et al., 2009; Salmoirago-Blotcher et al., 2016; Smeijers, Szabo, & Kop, 2016; Smeijers et al., 2015; Summers et al., 2010). Finally, an extensive cardiologic cohort study with 1750 TTC patients (89.9% female) showed that patients with TTC present a higher prevalence of former or chronic neurologic or psychiatric disorders (Templin et al., 2015). However, long-term effects of TTC on mental well-being and QoL have not yet been examined.

Against this ambiguous background, this study aimed at a better understanding of the long-term impacts of TTC on patients' mental and physical QoL in comparison to patients with a history of MI as well as to normal reference values. In a cross-sectional approach, 68 patients with a history of TTC and MI, respectively, filled in a comprehensive catalogue of standardized questionnaires capturing concurrent QoL, depression, anxiety, chronic stress, social support and resilience scores. Due to more recent randomized-controlled trials, arguing an underestimation of the severity of TTC, we hypothesized that psychosocial and physical long-term outcomes in patients with a history of TTC are at least similar to those of MI, we also examined the predictive value of the amount of stress events prior to

disease onset for long-term outcomes in psychosocial and physical variables (Ionescu et al., 2010; Scally et al., 2018).

Methods

Within this multi-centered, case-control study biographical, psychosocial and physical characteristics of TTC and MI patients were examined by means of a postal survey. Data from these questionnaires was complemented with cardiac markers and disease classifications at disease onset (LVEF, creatine kinase (muscle/brain) (CK, CK-MB), New York Heart Association Functional Classification (NYHA)), which were collected from the local databases. The study protocol followed the principles of GCP/Helsinki and was approved by the corresponding institutional review boards (Technische Universitaet, Munich, Universitaet zu Luebeck).

Sample

The total sample of 136 patients comprised 68 patients diagnosed with TTC and 68 post MI patients who received diagnostics and treatment in the cardiological departments Deutsches Herzzentrum and Klinikum Rechts der Isar, Technische Universitaet, Munich, as well as Segeberger Kliniken and Medizinische Klink II, Universitaetsklinikum Schleswig-Holstein, Campus Luebeck (see Table 1). TTC and MI patients were matched according to age and sex.

Table 1. Sample characteristics.

	TTC (n = 68)	MI (n = 68)	*p*
Center			.2††
Deutsches Herzzentrum, Technische Universitaet, Munich, *n*	21	22	
Klinikum rechts der Isar, Technische Universitaet, Munich, *n*	9	12	
Bad Segeberger Kliniken, *n*	10	16	
Medizinische Klinik II, Universitaetsklinkum Schleswig-Holstein, Campus Luebeck, *n*	28	18	
Age, *Mean (SD), years*	68.3 (11.8)	69.2 (10.6)	.65†
Sex, *n* (male/female)	4/64	4/64	
Number of children, *Median (IQR)*	2 (1)	2 (2)	.79 ††
Current living situation (multiple answers possible)			
Living alone, *n*	22	23	.86†††
With a partner, *n*	42	41	.86†††
With children, *n*	15	12	.68 †††
In a shared apartment, *n*	1	0	.31†††
With parents/parents in law	1	0	1.0†††
Current working situation			
full-time, *n*	6	5	
part-time, *n*	3	6	
unemployed, *n*	2	2	
incapacitated for work, *n*	1	3	
within the own household, *n*	15	7	
retired,	30	29	
others, *n*	5	2	.63††
Time span since diagnosis *Mean (SD), months*	58.32 (27.37)	49.92 (28,99)	.07†††

Note: Due to their epidemiological characteristics, the average age of the total sample was relatively high (M = 68.7 years). As to be expected, the female sex prevails (94%).
† T-Test †† Chi-square-Test ††† Mann-Whitney-Test

Inclusion criteria

TTC patients were considered for participation if they fulfilled the Mayo Clinic's diagnostic criteria for stress-induced cardiomyopathy, as follows: (1) transient hypokinesis, akinesis, or dyskinesis of the left ventricular mid segments with or without apical involvement; regional wall motion abnormalities extending beyond a single epicardial vascular distribution with a stressful trigger 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 a pheochromocytoma or myocarditis (Madhavan & Prasad, 2010).

In conformity with the American Heart Association, the inclusion criteria for MI patients were as follows: (1) Symptoms of myocardial ischemia (2) new ischemic ECG changes, (3) development of pathological Q waves (4) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology (5) identification of a coronary thrombus by angiography or autopsy (Schofer et al., 2014; Thygesen et al., 2018).

Procedure

Patients with a history of TTC or MI, who met all inclusion criteria and none of the exclusion criteria, were identified within local databases through the local study personnel. Both patient groups were matched according to age and sex. All data was de-identified with codes only available to the study coordinator. Potentially eligible patients were called, informed about the purpose of the study, and asked for permission to send the survey battery, containing 10 standardized, validated questionnaires (only 6 reported here; for other questionnaires, see Goetzmann et al., submitted). Non-responders were called again and reminded to complete the questionnaire after 4 weeks.

Measures

Disease-related QoL was assessed by using the short form (SF-12) questionnaire and the Kansas City Cardiomyopathy Questionnaire (KCCQ). The SF-12 is a validated and internationally established questionnaire, examining physical and mental related QoL (PCS/MCS) during the preceding 4 weeks, while KCCQ serves as a self-assessment tool to measure heart-failure-specific QoL. It consists of 23 items, rating six domains (e.g. physical restrictions, symptom frequency, social restrictions, self-efficacy, or QoL). These domains are summarized into the subscales functional status and clinical summary. Both tools fulfil the criteria for test quality with an internal consistency of Cronbachs $\alpha = .8$ for SF-12, respectively Cronbachs $\alpha = .93$ for KCCQ (Bullinger, 2000; Faller et al., 2005; Green, Porter, Bresnahan, & Spertus, 2000; Lim & Fisher, 1999; Müller-Nordhorn, Roll, & Willich, 2004; Resnick & Parker, 2001; Ware, Kosinski, & Keller, 1996). Presence of depression and/or anxiety was assessed by means of the Patients Health Questionnaire (PHQ-4). The ultra-brief, but reliable and valid version of the PHQ-4, that examines depression and anxiety with four items in accordance with the Diagnostic and Statistical Manual of Mental Disorders (Khubchandani, Brey, Kotecki, Kleinfelder, & Anderson, 2016; Kroenke,

Spitzer, Williams, & Lowe, 2009; Michal et al., 2015; Vahia, 2013). Stress within the previous three months was evaluated by using the 'Screening Scale for Unspecific Chronic Stress' (SSCS) as obtained from the 'Trier Inventory for Chronic Stress' (TICS). It's internal consistency (Cronbachs α of .91) and reliability (.84 – .91) is considered very good (Petrowski, Paul, Albani, & Brähler, 2012; Schulz & Schlotz, 1999). The 'Resilience Scale' (RS-5) was used as a validated tool to measure resilience, as the individual's salutogenic ability, with 5 items. 'RS-5' was psychometrically reviewed with an internal consistency of Cronbachs α = .80 (Schmalbach et al., 2016; Wagnild & Young, 1993). Finally, the ENRICHD Social Support Instrument (ESSI) served as a validated tool to quantify social support (Cordes, Herrmann-Lingen, Büchner, & Hessel, 2009; Kendel et al., 2011; Roest et al., 2013).

Furthermore, the following socio-demographic characteristics were also collected: number of children, housing situation, and current working situation (see Table 1).

Statistical analysis

All statistical analyses were performed by means of IBM SPSS Statistics 25, with a p-value ≤ 0.05 indicating statistical significance. To investigate possible differences between TTCs, MIs and norms, Bonferroni-corrected independent samples T-Tests were performed for normally distributed, continuous variables; Mann-Whitney-U Tests for non-normally distributed, continuous variables, and Chi-square tests for categorical variables. Separate linear regression analyses were performed to investigate whether the variance in psychosocial variables (i.e. disease related QoL, depression and anxiety, chronic stress, social support and resilience) at survey time could be explained by the number of life events before disease onset (see Table 3).

Results

Sample characteristics

Both patient collectives were comparable in regard to age, sex, (male = 8) and further socio- demographic characteristics (see Table 1). Mean time span since diagnosis was 58.32 months, SD = 27.37 in TTCs and 49.92 months, SD = 28.99 in MIs (p = .07). Within both groups more than half of the patients reported a stressful life event prior to their disease (TTC: 69.1%; MI: 60.3%) (see Table 1).

As indicated in Table 2, post TTC and MI patients scored lower than norms in both the mental and physical SF-12 subscales (p's< 0.05), while no significant differences between the two patient groups emerged (Nübling, Andersen, & Mühlbacher, 2006). Similarly, heart-failure-specific QoL (KCCQ) was significantly lower in TTC patients and post MI patients as compared to norms (p's< 0.05) (Faller et al., 2005). Again, there was no difference between the two patient groups detected. Furthermore, anxiety and depression scores (PHQ-4) were significantly higher in both patient collectives than in norm samples (p's< 0.05) (Lowe et al., 2010). Again, no differences could be observed between the two patient collectives. In addition, patients with a history of TTC or MI did not differ with regard to chronic stress (SSCS – TICS) but reported significantly higher chronic stress scores than the norm sample (p's< 0.05) (Schulz & Schlotz, 1999). Interestingly, resilience

Table 2. Comparison between TTC, MI, and norm values.

	TTC		MI		TTC vs. MI	Norm		TTC vs. Norm	MI vs. Norm
	M	*SD*	*M*	*SD*	*p**	*M*	*SD*	*p**	*p**
SF-12									
SF-12-PCS	47.23	11.91	46.81	11.58	.99	50	10	≤ .05	≤ .05
SF-12-MCS	41.55	17.21	43.47	16.2	.75	50	10	≤ .05	≤ .05
KCCQ									
'functional status score'	45.1	9.5	45.17	9.87	.33	87	12	≤ .05	≤ .05
'clinical summary score'	68.56	11.97	67.59	9.43	.47	80	15	≤ .05	≤ .05
PHQ-4									
'anxiety'	1.94	1.6	1.56	1.6	.06 ††	.94	1.52		
'depression'	1.77	1.52	1.3	1.39	.09 ††	.82	1.1		
PHQ-4 sum	3.71	2.94	2.85	2.79	0.1	1.76	2.06	≤ .05	≤ .05
RS-5	28.63	5.42	29.8	5.61	.13	27.20	5.2	≤ .05	≤ .05
TICS-SSCS	57.5	16.53	53.14	15.34	.11	50	10	≤ .05	≤ .05
ESSI	21.51	3.28	21.02	4.30	.9	20.47	4.05	1.0	1.0

Note: Norm values have been withdrawn from standardized validation studies; since the PHQ-4 sub scores are not normally distributed, a statistical comparison to the norm sample was not indicated.

Abbreviations: SF-12, Short Form-12; SF-12-PCS, Short Form-12 Physical Component Score, SF-12-MCS, Short Form-12 Mental Component Score, KCCQ, Kansas City Cardiomyopathy Questionnaire; PHQ-4, Patient Health Questionnaire; RS-5, Resilience Scale-5; TICS-SSCS, Trier Inventory for Chronic Stress-Screening Scale for Unspecific Chronic Stress; ESSI, ENRICHD Social Support Instrument.

* Bonferroni-corrected *t*-Test

†† Mann-Whitney-Test

values (RS-5), were significantly higher in TTC and MI patients as compared to normative values (p's< 0.05), while again, resilience scores did not differ between the two patient groups (Schmalbach et al., 2016). Regarding social support (ESSI), no significant

Table 3. Physical parameter during acute phase and reported life events prior to the onset of the disease.

		TTC n (%)	MI n (%)	p-value
Physical parameters during acute phase				
Chest pain (%)		66.1	93.75	.00 ††
NYHA Stage (%)				1.6††
	I	45.6	50.00	
	II	15.8	17.4	
	III	15.8	17.4	
	IV	15.8	13.00	
LVEF (%)				1.6††
	< 30%	6.8	8	
	30–50%	83.1	50	
	> 50%	11.67	42.0	
CK (U/l) Mean (SD)		288.42 (442.46)	667.1 (911,06)	.00†††
CK-MB (U/l) Mean (SD)		47.65 (50.03)	94.34 (94.5)	.00†††
Life events prior to the onset of the disease				
Recall of life event, *n (%)*		47 (69.1%)	41 (60%)	.25†
Amount of life events Median (IQR)		1 (1.25)	1 (2)	.44††
Occupational stress		15 (22.1%)	18 (26.5%)	.73††
Conflicts at work		4 (5.9%)	5 (7.4%)	.35††
Stress within the family		19 (27.9%)	23 (33.8%)	.66††
Conflicts within the family		16 (23.5%)	9 (13.2%)	.02††
Strong, positive experiences		2 (2.9%)	5 (7.4%)	.68††
Strong, annoying experiences		11 (16.2%)	18 (26.5%)	.76††
Strong, joyful experiences		3 (4.4%)	8 (11.8%)	.68††
Cases of death within the immediate surroundings		9 (12.9%)	10 (14.3%)	.93††
Further life events		17 (24.3%)	12 (17.1%)	.9††

Abbreviations: NYHA, New York Heart Association; LVEF, left-ventricular ejection fraction; CK, creatine kinase; CK-MB, creatine kinase-muscle/brain.

† T-Test

†† Chi-square-Test ††† Mann-Whitney-Test

Table 4. Linear regression analysis for the predictor 'number of life events'.

	b		SE		β		p-value	
Criterion variable	TTC	MI	TTC	MI	TTC	MI	TTC	MI
SF-12								
SF-12-PCS	.00	.05	1.2	1.1	.06	−.22	.67	.13
SF-12-MCS	.09	.12	1.43	.99	−.3	−.35	.03	.01
KCCQ								
'functional status score'	.00	.01	1.38	1.1	−.02	−.1	.89	.45
'clinical summary score'	.0	.05	2.29	1.51	.02	−.21	.89	.13
PHQ-4 sum score	.03	.11	.3	.24	.17	.33	.19	.01
RS-5	.02	.02	.54	.5	−.14	−.13	.26	.31
TICS-SSCS	.20	.08	.96	.84	.45	.29	.00	.02
ESSI	.09	.02	.32	.38	−.3	−.14	.02	.27

Abbreviations: SE, Standard Error; SF-12, Short Form-12; SF-12-PCS, Short Form-12 Physical Component Score, SF-12-MCS, Short Form-12 Mental Component Score, KCCQ, Kansas City Cardiomyopathy Questionnaire; PHQ-4, Patient Health Questionnaire-4; RS-5, Resilience Scale-5; TICS-SSCS, Trier Inventory for Chronic Stress-Screening Scale for Unspecific Chronic Stress; ESSI, ENRICHD Social Support Instrument

differences were observed, neither between patient groups nor between patients and norms (Cordes et al., 2009).

A majority of patients recalled the occurrence of life events prior to disease onset (TTC: 69.1%, MI: 60%). Both positive and negative events were reported, mainly referring to the areas family and occupation. Significant differences between TTCs and MIs could only be found for one response option ($p = .02$); TTCs reported almost twice as often 'conflicts within the family' prior to disease admission (Table 3).

Explorative linear regression analyses were performed to investigate whether the number of life events prior to disease onset has an influence on the collected psychosocial variables. In TTCs and MIs the number of life events significantly predicted SF-12-MCS and TICS-SSCS scores. Additionally, the number of life events significantly predicted ESSI scores in TTCs and PHQ-4 sum scores in MIs, respectively (see Table 4).

Discussion

This study aimed at a better understanding in psychosocial and physical long-term outcome of TTC patients in comparison to MI patients. Furthermore, both patient groups were compared to those of normative reference values. Within both patient groups, the history of a heart disease, be it TTC or MI, was associated with decreased physical (SF-12-PCS, KCCQ) and mental (SF-12-MCS, TICS-SSCS) QoL, as compared to norm samples. KCCQ summary scores of both patient groups were equivalent to those of MI patients with a LVEF lower than 40%, which implies a considerable restriction of the cardiac function (Pettersen, Kvan, Rollag, Stavem, & Reikvam, 2008). Also, the anxiety and depression sum score (PHQ-4) was significantly increased in both patient groups as compared to normative values, indicating mild symptoms (Kroenke et al., 2009). Therefore, our findings support the results of recent studies suggesting that patients with a history of TTC and MI are, faced with severe negative long-term mental and physical effects (Compare et al., 2014; Scally et al., 2018; Templin et al., 2015).

A bi-directional association between depressive symptoms and CAD is well established and first studies indicate a related link for TTCs. Further studies reported that the

relationship between depression and MIs might be even stronger in female patients than it is for males (Doyle et al., 2015; Naqvi, Naqvi, & Merz, 2005). A similar association could also be conceivable for TTC patients. Considering the sex distribution within the present sample, this would give a hint to the decreased mental QoL in MIs as well as in TTCs, compared to norm samples. Notably, not only the majority of TTC patients (69.1%), but also 60% of MI patients were recalled stressful life events prior to disease onset. Additionally, to acute stressors prior to disease onset, also higher levels of chronic stress (TICS-SSCS) could be detected in patients with TTC as well as in post MI patients, compared to norm samples. Chronic stress includes the perception, appraisal, and response to repetitive, emotionally or physiologically challenging events or stimuli (Lazarus, 2006; McEwen, 2007). Gender differences in coping strategies (e.g. problem or emotion focused) for repetitive challenges have been described, with women being more likely to use emotional coping strategies and beyond that, tend to appraise stressors as more severe as men (Diehl, Coyle, & Labouvie-Vief, 1996; Sieverding, Kendel, & Böhmer, 2004; Tamres, Janicki, & Helgeson, 2002). This gains importance, because 96% of our sample were female patients and interestingly, only the stressor 'conflicts within the family' was reported more frequently in TTCs (see Table 3).

Since TTC is associated with an excessive activation of the sympathetic nervous system, differences in coping strategies and problem perception might help to explain the higher prevalence of TTC in women. Remarkably, the number of life events prior to disease onset was significantly related to perceived chronic stress and mental QoL in both patient collectives. Recent studies reported that especially the exposure to repeated stressful life events was related to the onset of TTC (Rosman, Dunsiger, & Salmoirago-Blotcher, 2017; Wallström, Ulin, Määttä, Omerovic, & Ekman, 2016). Authors argue that long-term stressful conditions might have led to an increased vulnerability to further emotional or physical stressors that in turn triggered the development of TTC. This suggests that the amount of life events might not only be a risk factor for the appearance of TTC, but also for long-term mental well-being. Therefore, maladaptive coping may not only contribute to the development of the heart disease but also to the impaired QoL many years after disease admission, as observed in our study. Further, the patients' perception of disease severity within the acute phase of TTC due to frightening symptoms, mimicking an acute coronary syndrome, could also be considered as a potential source of maladaptive coping. This explicitly fearsome perception of stress could be meaningful for the mental wellbeing of MIs and TTCs, also in the long-term.

Both patient groups displayed similar but significantly higher-than-normal scores of resilience. At a first glance, these results appear to be counterintuitive: Resilience, generally conceived as personality trait, would rather be considered a protection factor for the development of TTC and MI. A possible explanation could be the phenomenon of 'post-traumatic growth', defined as positive personal change through the experience of a striking traumatic or adverse life event (Cordova & Andrykowski, 2003; O'Leary & Ickovics, 1995; Roebuck, Furze, & Thompson, 2001).

The following limitations of our study need to be considered. Even though sex distribution of TTC patients (96% females) reflects sex distribution within the TTC population, the high proportion of female patients may have introduced some bias when comparing the results to 'equally sex distributed' normative values (Templin et al., 2015).

This might, be the case regarding the comparison of depression scores of our mostly female patient collectives and norm samples, because the prevalence of depression is higher among women than men, with a risk ratio of approximately 2:1 (Kessler, 2003). Furthermore, the over-representation of (elderly) female patients diminishes the generalizability to MI patients, who are predominantly male. Given the high variability of outcomes (see Table 3), which is in line with previous studies, a larger number of male and female participants would have been desirable in order to enhance the statistical power for the analyses (Compare et al., 2014; Rosman et al., 2017; Sobue et al., 2017). Considering the low TTC prevalence of only 0.07–3% in patients presenting with an acute coronary syndrome, however, the sample size of 68 TTC patients is comparably high and four study centers were necessary to retrieve these numbers in a reasonable time frame. In addition, matching was done for age and sex, but not for the time point of diagnosis. However, the time span between diagnosis and survey participation did not differ significantly between groups ($p = .07$). Nonetheless, the large variety of time periods between disease onset and the present survey may have had an impact on the individuals' answers; for example, a recall bias could have influenced the list of stress events prior to disease onset. Therefore, prospective studies are warranted to further consolidate our findings. Finally, due to the cross-sectional design of this study, baseline values of psychosocial variables as well as physiological risk factors (such as hypertension or diabetes) before and at disease onset were not available. Therefore, the possible impact of mental and physical conditions prior to the disease onset and the impact of the disease itself cannot be differentiated, and causal relationships cannot be drawn.

In summary, it can be concluded that patients with a history of TTC showed considerably reduced emotional and physical wellbeing on average 4.9 years after disease onset, which is comparable to that of MIs (Roebuck et al., 2001). Both patient groups, TTC and MI, reported higher chronic stress levels as well as reduced health related QoL. Whether this is associated with maladaptive coping strategies in regard to potential life stressors needs to be tested in further studies.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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