

RESEARCH ARTICLE

Early evolution of psychological functioning after Takotsubo syndrome: A prospective cohort study

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Abstract

Background: Although ventricular function usually recovers rapidly after Takotsubo syndrome (TTS), little is known about the early evolution of psychological functioning.

Objectives: In this study, we examined longitudinal changes across multiple psychological domains during the first month in patients with TTS, patients with acute myocardial infarction (AMI), and healthy controls (HC).

Methods: Eighty-five participants (37 TTS, 23 AMI, and 25 HC) completed psychological assessments during the acute phase and 30 days later. The assessment

included symptoms of anxiety and depression, anger, coping strategies, emotion regulation, resilience and worry. Longitudinal changes were evaluated using linear mixed-effects models including fixed effects for group, time, and the group $\times$ time interaction, with a random intercept for participants.

Results: A significant group $\times$ time interaction was observed for anger-in control, with patients with AMI showing a greater increase over time than HC; this interaction remained significant after false discovery rate (FDR) correction for multiple testing. An interaction was also observed for cognitive coping in the primary analysis, but it did not remain significant after FDR correction and was therefore considered exploratory.

Conclusion: Most psychological outcomes did not show statistically significant longitudinal changes during the first month after TTS. These findings highlight the importance of incorporating psychological assessment into routine follow-up after TTS.

Keywords: Takotsubo syndrome; Longitudinal study; Emotion regulation; Resilience; Acute myocardial infarction

1. Introduction

Although ventricular function usually recovers within days or weeks, Takotsubo syndrome (TTS) is no longer considered a benign condition, as it may be associated with serious in-hospital complications and long-term outcomes comparable to those of acute myocardial infarction (AMI). Moreover, its underlying pathophysiology remains complex and incompletely understood, with recent molecular research identifying additional potential pathways involved in the syndrome. Despite advances in understanding the clinical and biological features of TTS, much less is known about patients' psychological recovery following the acute event.¹⁻³

Over the last decade, studies have reported a higher prevalence of psychiatric disorders among patients with TTS, together with greater levels of anxiety, depression, and psychological distress compared with both other cardiac populations and healthy individuals.^{4,5} Nevertheless, the available evidence remains limited. A systematic review by Galli *et al.*⁶ highlighted important methodological limitations across published studies, preventing firm conclusions regarding the role of psychological factors in TTS. More recently, Leissner *et al.*⁷ also pointed out the scarcity of longitudinal studies examining how these psychological characteristics evolve following the acute event.

Furthermore, most previous research has focused primarily on anxiety, depression, and health-related quality of life. Other psychological dimensions that may

be equally relevant, including emotion regulation, coping strategies, and positive psychological resources such as resilience, have received considerably less attention. Resilience has been proposed as a positive psychological resource with potential cardioprotective effects. Kubzansky *et al.*⁸ suggested that psychological well-being may influence cardiovascular health through direct effects on neurobiological pathways, indirect effects mediated by healthier behaviors, and the promotion of psychosocial resources that buffer the physiological consequences of stress. Consistent with this hypothesis, positive emotions and psychological well-being have been associated with reduced activation of the hypothalamic-pituitary-adrenal axis, lower cortisol levels, improved immune function, and greater adoption of healthy lifestyle behaviors.^{8,9}

Understanding whether these psychological characteristics remain stable or begin to change during the first weeks after TTS is clinically relevant. If psychological functioning follows a trajectory different from cardiac recovery, this would support the need to extend psychological assessment beyond the acute hospital phase and could provide further insight into the mechanisms underlying the syndrome.

The present study is part of the multicenter Tako-Tsubo Brain Project. Its aim was to investigate the longitudinal evolution of psychological characteristics during the first month following TTS and to examine differences in these trajectories across patients with TTS, patients with AMI, and healthy controls (HC).

2. Materials and methods

2.1. Study design

This study is part of the Tako-Tsubo Brain Project, a multicenter research project conducted in nine hospitals in Spain. The project included two phases. The first was a retrospective study focused on the characterization of psychological variables associated with TTS.¹⁰ The second phase was based on prospective recruitment and included psychological assessment during the acute phase (unpublished results). The present study is a prospective longitudinal observational cohort study with comparison groups examining the early evolution of psychological variables between baseline and the 30-day follow-up assessment.

2.2. Participants

Participants were recruited as part of the prospective phase of the Tako-Tsubo Brain Project, a prospective longitudinal observational cohort with comparison group study conducted across nine hospitals in Spain between June 2018 and December 2024. For patients with TTS and AMI, the baseline psychological assessment was performed during the index hospitalization once they were clinically stable. HC completed the baseline assessment at the time of enrollment.

The present study represents the longitudinal cohort of the larger prospective Tako-Tsubo Brain Project and was specifically designed to examine early psychological trajectories between the acute assessment and the 30-day follow-up. Accordingly, the analytical cohort for the present longitudinal substudy comprised participants for whom sufficient 30-day psychological information was available. After data collection, to minimize participant exclusion due to isolated missing questionnaires, participants were included if they had completed at least three psychological questionnaires at the 30-day follow-up assessment. Notably, no participant completed exactly two or three questionnaires at follow-up (Table S5).

Patients with TTS were recruited across all participating centers, whereas all patients with AMI and all HC were recruited at Hospital Universitario 12 de Octubre. HC were recruited through non-probability community-based sampling. Potential HC were approached by members of the multidisciplinary research team, including cardiologists, psychologists, and research nurses, who were also responsible for recruiting participants with TTS and AMI according to the study protocol.

Participants were eligible if they met the following criteria: (i) a confirmed diagnosis of TTS for the case group, absence of known cardiovascular or cerebrovascular

disease (except cardiovascular risk factors such as hypertension) for HC, or a confirmed diagnosis of type 1 AMI¹ for the AMI group; (ii) age ≥ 18 years; (3) provision of written informed consent; (4) adequate understanding and fluency in Spanish; and (5) sufficient cognitive capacity to complete the psychological assessment.

For patients with TTS, the diagnosis required a clinical presentation compatible with acute coronary syndrome, absence of obstructive coronary artery disease on early coronary angiography, transient regional left ventricular dysfunction, and no alternative diagnosis. For patients with AMI, the diagnosis including a rise and/or fall in cardiac troponin with at least one value above the 99th percentile, together with electrocardiographic changes and angiographic evidence of acute coronary thrombosis.

2.3. Variables and instruments

The variables analyzed in this study are as follows:

- (i) *Baseline demographic variables* included age, sex and educational level.
- (ii) *Baseline clinical variables* included cardiovascular risk factors (hypertension, dyslipidemia, and diabetes), menopause, history of psychological disorders, and psychotropic medication.
- (iii) *Lifestyle variables* included smoking status and alcohol consumption. Clinical information for patients with TTS and AMI was extracted from medical records. For HC, medical history and lifestyle information were obtained through a structured self-report questionnaire specifically developed for the study, as access to medical records was not available.

Psychological assessment and instruments utilized in this study are as follows:

- (i) *Negative psychological factors*
 - Anxiety and depression symptomatology: *The Hospital Anxiety and Depression Scale (HADS)*.^{11,12} The HADS is a 14-item self-report questionnaire consisting of two 7-item subscales measuring anxiety (HADS-A) and depression (HADS-D). Items are rated on a 4-point Likert scale (0–3), with higher scores indicating greater symptom severity.
 - Anger dimensions (anger trait, anger-in and anger-out expression, anger-out and anger-in control): *State-Trait Anger Expression Inventory-2 (STAXI-2)*.^{13,14} The STAXI-2 is a self-report

¹ Type 1 AMI refers to spontaneous acute myocardial infarction caused by a primary coronary event, such as atherosclerotic plaque rupture or erosion leading to intraluminal thrombus formation.

questionnaire that evaluates different dimensions of anger, including state anger, trait anger, anger expression, and anger control. Items are rated on a 4-point Likert scale, with higher scores indicating greater levels of the construct assessed.

- Coping styles (cognitive, avoidance, social support, and spiritual): Brief COPE (COPE-28).^{15,16} This 28-item self-report questionnaire evaluates 14 coping strategies, each measured by two items. Responses are rated on a 4-point Likert scale ranging from 1 (“I haven’t been doing this at all”) to 4 (“I’ve been doing this a lot”), with higher scores indicating greater use of each coping strategy.
- Emotion regulation strategies (lack of emotional attention, emotional confusion, emotional rejection, emotional lack of control and emotional life interference): *Difficulties in Emotion Regulation Scale* (DERS).^{17,18} The DERS consists of 28 items assessing six domains of emotion regulation difficulties: lack of emotional attention, emotional confusion, emotional rejection, emotional life interference, emotional lack of control and emotion regulation. Items are rated on a 5-point Likert scale ranging from 1 (“almost never”) to 5 (“almost always”), with higher scores indicating greater difficulties in emotion regulation.
- Worry: *Penn State Worry Questionnaire* (PSWQ).^{19,20} The PSWQ is a 16-item self-report questionnaire designed to assess the tendency to engage in excessive and uncontrollable worry. Items are rated on a 5-point Likert scale, with higher scores indicating greater levels of trait worry.

(ii) *Positive psychological factors*

- Resilience: *Brief Resilience Scale* (BRS).^{21,22} The BRS is a 6-item self-report questionnaire that measures the ability to recover or “bounce back” from stressful experiences. Items are rated on a 5-point Likert scale, and higher scores indicate greater resilience.

2.4. Participating hospitals

The study involved nine participating hospitals within the Tako-Tsubo Brain Project network in Spain: Hospital Universitario 12 de Octubre (Madrid), Hospital Clínico San Carlos (Madrid), Hospital General Universitario Gregorio Marañón (Madrid), Hospital Universitario de Getafe (Madrid), Hospital Universitario Fundación

Jiménez Díaz (Madrid), Hospital Universitario Miguel Servet (Zaragoza), Hospital Universitari Vall d’Hebron (Barcelona), Hospital Clínico Universitario Virgen de la Arrixaca (Murcia), and Hospital Universitario Marqués de Valdecilla (Santander).

2.5. Data analysis

2.5.1. Statistical analysis

Participants were considered to have completed the 30-day follow-up if valid data were available for at least three psychological questionnaires administered at the follow-up assessment. This criterion was established to ensure sufficient longitudinal psychological information across the assessment battery while minimizing participant exclusion due to isolated missing questionnaire data (Table S5).

Because the study evaluated multiple psychological constructs using separate validated instruments, each outcome was analyzed independently using a linear mixed-effects model. To account for multiple testing across the 19 group $\times$ time interaction tests, p-values were adjusted using the Benjamini–Hochberg false discovery rate (FDR) procedure.

Of the 234 participants initially recruited (78 TTS, 78 AMI, and 78 HC), 85 participants (37 TTS, 23 AMI, and 25 HC) had sufficient 30-day psychological data to meet this criterion and comprised the longitudinal analytical cohort. The remaining 149 participants had insufficient or no 30-day follow-up data and were not included in the primary longitudinal analyses (Figure 1).

Two distinct sources of missing data should therefore be distinguished: absence of sufficient 30-day data for inclusion in the longitudinal cohort and questionnaire-level missingness among participants included in that cohort. Linear mixed-effects models with maximum-likelihood estimation allowed participants within the longitudinal cohort with incomplete data for individual questionnaires to contribute all available observations for the corresponding outcome; however, this approach was not intended to account for absence of follow-up data among participants outside the longitudinal cohort.

Follow-up procedures were substantially affected by operational disruptions during the COVID-19 pandemic. Consequently, for a substantial proportion of participants without 30-day data, the absence of follow-up reflected the inability to perform or initiate the scheduled follow-up assessment rather than documented refusal to participate. However, the specific reason for missing follow-up was not prospectively recorded at the individual participant level.

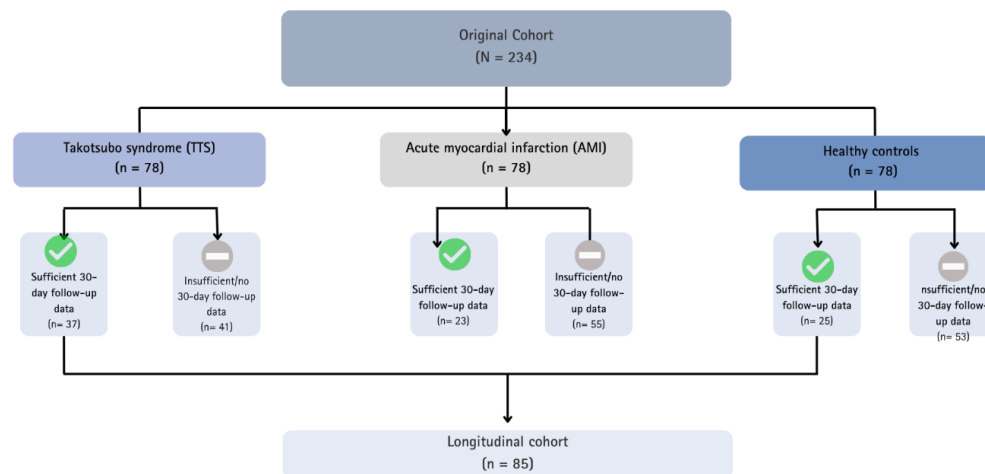


Figure 1. Flow diagram of participant recruitment and availability of 30-day follow-up data. Of the 234 participants recruited at baseline (78 Takotsubo syndrome [TTS], 78 acute myocardial infarction [AMI], and 78 healthy controls [HC]), 85 participants had sufficient psychological data at the 30-day follow-up (37 TTS, 23 AMI, and 25 HC) and comprised the longitudinal analytical cohort. Sufficient follow-up data were defined as the availability of at least three psychological questionnaires at the 30-day assessment.

To assess the potential impact of follow-up losses, participants who completed the 30-day follow-up were compared with those lost to follow-up. Independent-samples *t*-tests were used for continuous variables and chi-square tests for categorical variables (Table S1). For attrition analyses, Cohen's *d* with 95% confidence intervals was calculated for continuous variables and Cramér's *V* for categorical variables to quantify the magnitude of differences between participants with sufficient and insufficient/no follow-up data.

Baseline sociodemographic and clinical characteristics of participants included in the longitudinal analyses were compared across study groups using one-way analyses of variance (ANOVA) for continuous variables and chi-square tests for categorical variables. Cramér's *V* was calculated as a measure of effect size for categorical variables.

Longitudinal changes in psychological variables were analyzed using linear mixed-effects models fitted separately for each psychological outcome. Each model included study group (TTS, AMI, and HC), time (baseline and 30-day follow-up), and the group $\times$ time interaction as fixed effects, together with a random intercept for each participant to account for within-subject correlations arising from repeated measurements. Parameters were estimated using full maximum likelihood (ML), allowing participants with incomplete data for individual questionnaires within the longitudinal sample to contribute all available observations for the corresponding outcome.

To evaluate the robustness of the findings, additional adjusted models were fitted including one clinically relevant covariate at a time (age, sex, alcohol consumption, and smoking status). Estimated marginal means (EMMs) with 95% confidence intervals were calculated for each study group and assessment time to facilitate interpretation of longitudinal changes (Table S2).

In addition, multivariable models simultaneously including age, sex, smoking status, and alcohol consumption were fitted for anger-in control and cognitive coping to further assess the robustness of the observed group $\times$ time interactions. Variance inflation factors were examined to assess collinearity among the included covariates.

Model diagnostics were examined for the anger-in control and cognitive coping models, both before and after simultaneous covariate adjustment. Residual distributions were assessed using Q–Q plots, and residuals versus fitted values were examined to assess residual variance. Participant-level estimates were also examined.

2.5.2. Missing data management

For psychometric instruments, mean imputation was applied when the number of missing items did not exceed predefined thresholds: COPE-28 (≤ 3 items), DERS (≤ 3 items), PSWQ (≤ 2 items), HADS (≤ 2 items), and STAXI-2 (≤ 3 items). Mean imputation was restricted to missing items within an otherwise completed psychometric instrument and was not used to replace entirely missing questionnaires.

or missing follow-up assessments. Questionnaire-level missingness was handled through the outcome-specific linear mixed-effects models using available observations. The availability of completed psychological questionnaires at baseline and at the 30-day follow-up is reported in Tables S3 and S4, respectively.

All tests were two-tailed and statistical significance was established at $p < 0.05$. Statistical analyses were performed using Stata Statistical Software, Release 16 (StataCorp, College Station, TX, USA) for the linear mixed-effects models and IBM SPSS Statistics version 21 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Participant characteristics and follow-up completion

Attrition analyses were conducted separately within each diagnostic group to compare participants with sufficient versus insufficient/no follow-up data at 30 days. Baseline psychological characteristics showed generally small standardized differences between these groups (Table S1). Among patients with AMI, participants with sufficient follow-up data were younger than those with insufficient/no follow-up data (65.26 ± 13.06 vs. 71.35 ± 8.74 years, $p = 0.019$; Cohen's $d = 0.60$, 95% CI 0.10–1.09), reported a higher frequency of alcohol consumption ($p = 0.022$), and included a lower proportion of postmenopausal women ($p = 0.021$). No other statistically significant differences in sociodemographic or clinical characteristics were observed. Overall, standardized differences in baseline psychological characteristics were generally small, although some differences were observed, and some degree of selective attrition cannot be excluded (Table S1).

Baseline sociodemographic and clinical characteristics are presented in Table 1. Smoking status and alcohol use differed across groups ($p = 0.003$, $V = 0.314$ and $p = 0.001$, $V = 0.460$, respectively), with both being more common among patients with AMI than among patients with TTS and HC. For clinical variables with substantial missingness among HC, inferential comparisons were restricted to the TTS and AMI groups, while healthy-control data were considered descriptive.

3.2. Longitudinal changes in psychological variables

Results from the linear mixed-effects models are presented in Table 2. Significant main effects of time were detected for anger-in control ($p = 0.036$) and lack of emotional attention ($p = 0.020$).

Between-group differences were observed for anxiety symptoms (TTS vs. HC, $p = 0.040$), resilience (TTS vs. HC,

$p = 0.006$), anger-in control (TTS vs. HC, $p = 0.032$), lack of emotional attention (AMI vs. HC, $p = 0.028$), emotional confusion (AMI vs. HC, $p = 0.044$), emotional rejection (AMI vs. HC, $p = 0.043$), and emotional lack of control (TTS vs. HC, $p = 0.032$).

A significant time $\times$ group interaction was identified for anger-in control in patients with AMI ($p < 0.001$), indicating a greater increase in anger-in control over the 30-day follow-up compared with HC (Figure 2). This interaction remained statistically significant after FDR correction for multiple testing (FDR-adjusted $p = 0.010$). An interaction was also observed for cognitive coping in the primary analysis ($p = 0.003$), with estimated marginal means showing a decrease over time in patients with AMI and an increase in HC; however, this interaction did not remain statistically significant after FDR correction (FDR-adjusted $p = 0.057$) and was therefore considered exploratory. No other group $\times$ time interactions remained statistically significant after FDR correction.

3.3. Sensitivity analyses

Sensitivity analyses using linear mixed-effects models adjusted separately for age, sex, alcohol consumption, and smoking status are presented in Table S2.

Hospital Anxiety and Depression Scale (HADS). Patients with TTS continued to report lower anxiety levels than HC after adjustment for age and sex, although this difference was attenuated after adjustment for alcohol consumption and smoking status. No differences were observed between patients with AMI and HC, and no time $\times$ group interactions emerged. Likewise, depressive symptoms remained comparable across the three groups, with no significant effects of time or group after adjustment.

State-Trait Anger Expression Inventory-2 (STAXI-2). For the anger-in control subscale, the main effect of time remained evident after adjustment for age, sex, and smoking status but was attenuated after adjustment for alcohol consumption. Patients with TTS also continued to show lower anger-in control than HC after adjustment for age, sex, and smoking status. In addition, patients with AMI exhibited a greater increase in anger-in control over time than HC, and this interaction remained significant across all adjustment strategies. No consistent time $\times$ TTS interaction was observed.

Brief Resilience Scale (BRS). Patients with TTS consistently reported lower resilience than HC after adjustment for age, sex, and smoking status, whereas this difference was no longer evident after adjustment for alcohol consumption. No statistically significant longitudinal effects or differences involving the AMI group were detected.

Table 1. Baseline sociodemographic and clinical characteristics of participants according to study group.

Variable	TTS (<i>n</i> = 37)	AMI (<i>n</i> = 23)	HC (<i>n</i> = 25)	<i>p</i>	Cramér's <i>V</i>
Age, mean (SD)	69.32 (10.99)	65.26 (13.06)	68.28(9.32)	0.387	
Female sex, <i>n</i> (%)	33 (89.2)	20 (87.0)	22 (88.0)	0.966	0.029
Education level, <i>n</i> (%)				0.133	0.302
Primary	18/28 (64.3)	9/18 (50.0)	5/22 (22.7)		
Secondary	1/28 (3.6)	2/18 (11.1)	3/22 (13.6)		
Vocational training (intermediate and higher level)	5/28 (17.9)	2/18 (11.1)	3/22 (13.6)		
Upper secondary education	0/28 (0.0)	1/18 (5.6)	2/22 (9.1)		
University	4/28 (14.3)	4/18 (22.2)	9/22 (40.9)		
Not reported	9	5	3		
Smoking status, <i>n</i> (%)				0.003	0.314
Never	28/37 (75.7)	8/23 (34.8)	12/21 (57.1)		
Active	2/37 (5.4)	9/23 (39.1)	2/21 (9.5)		
Ex-smoker (≥2 years)	7/37 (18.9)	6/23 (26.1)	7/21 (33.3)		
Not reported	0	0	4		
Alcohol use, <i>n</i> (%)				0.001	0.460
Never	31/34 (91.2)	6/13 (46.2)	9/17 (52.9)		
Active	3/34 (8.8)	7/13 (53.8)	8/17 (47.1)		
Not reported	3	10	8		
Menopause, <i>n</i> (%)	28/31 (90.3)	15/17 (88.2)	18/18 (100)	0.350	0.178
Not reported	2	3	4		
Hypertension, <i>n</i> (%)	26/37 (70.3)	16/23 (69.6)	2/4 (50.0)	0.954 ^a	0.007
Not reported	0	0	21		
Diabetes, <i>n</i> (%)	8/36 (22.2)	9/23 (39.1)	0/5 (0.0)	0.162 ^a	0.182
Not reported	1	0	20		
Dyslipidaemia, <i>n</i> (%)	18/37 (48.6)	17/23 (73.9)	1/4 (25.0)	0.054 ^a	0.249
History of psychological disorders, <i>n</i> (%)	12/37 (32.4)	5/23 (21.7)	0/1 (0.0)	0.371 ^a	0.115
Psychotropic medication, <i>n</i> (%)	15/37 (40.5)	8/23 (34.8)	-	0.656 ^a	0.058
Not reported	0	0	25		

Notes: Continuous variables are presented as mean (SD) and were compared using one-way ANOVA or Kruskal–Wallis tests, as appropriate. Categorical variables are presented as *n/N* (%), where *N* represents the number of participants with available data for each variable. ^aDue to substantial missingness among healthy controls, formal comparisons for these clinical variables were restricted to the TTS and AMI groups; healthy-control data are presented descriptively only. Categorical variables were compared using chi-square tests. Cramér's *V* is reported as a measure of effect size for categorical comparisons. Clinical variables for TTS and AMI participants were obtained from medical records, whereas corresponding data for healthy controls were self-reported.

Abbreviations: AMI: Acute myocardial infarction; HC: Healthy controls; SD: Standard deviation; TTS: Takotsubo syndrome.

Table 2. Linear mixed-effects analysis of psychological variables across baseline and 30-day follow-up according to study group

Questionnaire	TTS		AMI		HC		TTS vs HC (p)	AMI vs HC (p)	Time × TTS (p)	Time × AMI (p)	FDR-adjusted p
	Baseline mean (95% CI) (n = 37)	30 days mean (95% CI) (n = 37)	Baseline mean (95% CI) (n = 23)	30 days mean (95% CI) (n = 23)	Baseline mean (95% CI) (n = 25)	30 days mean (95% CI) (n = 25)	Time (p)				
HADS											
Anxiety	10.75 (9.56–11.94)	11.11 (10.04–12.18)	11.69 (9.64–12.36)	13.09 (11.73–14.44)	12.60 (11.30–13.90)	13.04 (11.74–14.34)	0.547	0.095	0.933	0.118	0.468
Depression	15.35 (13.90–16.81)	13.97 (12.63–15.31)	15.17 (13.48–16.87)	15.96 (14.26–17.66)	16.76 (15.13–18.39)	16.6 (14.97–18.23)	0.833	0.207	0.233	0.389	0.440
STAXI-2											
Anger trait	21.01 (18.96–23.07)	18.92 (16.90–20.94)	20.00 (17.43–22.57)	18.91 (16.35–21.48)	19.32 (16.86–21.78)	18.40 (15.94–20.86)	0.382	0.301	0.392	0.912	0.993
Anger-out expression	9.28 (8.37–10.18)	9.37 (8.50–10.26)	10.13 (9.01–11.25)	9.52 (8.40–10.64)	9.36 (8.29–10.43)	9.44 (8.37–10.51)	0.890	0.907	0.976	0.408	0.993
Anger-in expression	12.97 (11.96–13.98)	12.59 (11.61–13.58)	12.65 (11.40–13.91)	12.74 (11.48–13.99)	12.16 (10.96–13.36)	11.88 (10.67–13.08)	0.686	0.313	0.916	0.714	0.993
Anger-out control	17.60 (16.25–18.96)	17.89 (16.56–19.22)	19.95 (18.27–21.64)	20.13 (18.45–21.81)	18.12 (16.50–19.74)	18.32 (16.70–19.94)	0.810	0.631	0.934	0.983	0.993
Anger-in control	14.58 (13.00–16.16)	14.97 (13.42–16.52)	14.74 (12.77–16.71)	18.00 (16.03–19.96)	17.28 (15.39–19.17)	15.32 (13.43–17.20)	0.036	0.032	0.054	0.001	0.010
BRS											
Resilience	16.62 (15.06–18.17)	17.43 (15.91–18.95)	19.09 (17.16–21.02)	20.70 (18.77–22.62)	20.0 (18.15–21.85)	19.96 (18.11–21.81)	0.968	0.006	0.503	0.250	0.993
COPE-28											
Cognitive	25.08 (23.88–26.28)	25.61 (24.43–26.78)	26.83 (25.34–28.32)	23.10 (20.79–25.41)	25.75 (24.32–27.18)	27.42 (25.41–29.42)	0.158	0.481	0.423	0.003	0.057

(Cont'd...)

Table 2. (Continued)

Questionnaire	TTS		AMI		HC		TTS vs HC (p)	AMI vs HC (p)	Time × TTS (p)	Time × AMI (p)	FDR-adjusted p
	Baseline mean (95% CI) (n = 37)	30 days mean (95% CI) (n = 37)	Baseline mean (95% CI) (n = 23)	30 days mean (95% CI) (n = 23)	Baseline mean (95% CI) (n = 25)	30 days mean (95% CI) (n = 25)					
Avoidance	19.48 (18.30–20.67)	18.59 (17.42–19.77)	19.94 (18.47–21.42)	17.60 (15.42–19.77)	19.24 (17.83–20.66)	18.27 (16.37–20.17)	0.331	0.502	0.940	0.371	0.993
Spiritual	4.92 (4.19–5.66)	5.21 (4.49–5.94)	4.58 (3.66–5.50)	4.40 (3.11–5.70)	4.18 (3.29–5.05)	4.33 (3.19–5.47)	0.785	0.532	0.842	0.703	0.993
DERS											
Lack of emotional attention	9.97 (8.76–11.18)	10.0 (8.83–11.17)	7.26 (5.78–8.74)	7.22 (5.74–8.70)	9.56 (8.14–10.98)	7.76 (6.34–9.18)	0.020	0.028	0.072	0.116	0.468
Emotional Confusion	7.28 (6.39–8.16)	7.84 (6.99–8.69)	5.74 (4.656–6.82)	6.26 (5.18–7.34)	7.28 (6.24–8.32)	6.32 (5.28–7.36)	0.113	0.044	0.056	0.090	0.439
Emotional rejection	14.76 (12.38–17.14)	14.92 (12.61–17.23)	17.30 (14.38–20.23)	16.18 (13.16–19.21)	13.12 (10.31–15.93)	12.84 (10.03–15.65)	0.841	0.043	0.809	0.680	0.993
Emotional life interference	10.45 (9.17–11.73)	10.27 (9.04–11.49)	10.09 (8.53–11.64)	9.92 (7.23–10.21)	8.72 (7.23–10.21)	8.20 (6.71–9.69)	0.584	0.213	0.785	0.798	0.993
Emotional lack of control	17.37 (15.06–19.68)	16.86 (14.63–19.10)	14.96 (12.13–17.79)	14.45 (11.52–17.39)	13.48 (10.77–16.19)	13.56 (10.85–16.27)	0.956	0.461	0.758	0.784	0.993
Emotion regulation	59.87 (53.91–65.82)	59.89 (54.14–65.64)	55.35 (48.06–63.64)	53.88 (46.30–61.45)	52.16 (45.17–59.15)	48.68 (41.69–55.67)	0.364	0.536	0.486	0.722	0.993
PSWQ											
Worry	56.59 (52.50–60.68)	54.57 (50.55–58.59)	54.91 (49.81–60.01)	50.74 (45.64–55.84)	50.72 (45.83–55.61)	50.44 (45.55–55.33)	0.897	0.245	0.538	0.214	0.993

Notes: Values are presented as estimated marginal means (95% confidence intervals) derived from linear mixed-effects models. Longitudinal analyses were performed using mixed-effects linear regression with time (baseline vs. 30-day follow-up), group (TTS, AMI, and HC), and the time × group interaction included as fixed effects, and a random intercept for participants to account for within-subject correlations. P-values for group correspond to comparisons of TTS and AMI with healthy controls (reference group). Interaction p-values correspond to the time × group contrasts for TTS and AMI relative to healthy controls. To account for multiple testing across the 19 group × time interaction tests, p-values were additionally adjusted using the false discovery rate (FDR) procedure. Group sample sizes shown in the column headings represent the overall longitudinal analytical cohort and not the number of observations available for every individual outcome. The exact number of participants contributing data to each questionnaire at baseline and 30-day follow-up is reported in Tables S3 and S4.

Abbreviations: AMI: acute myocardial infarction; BRS: Brief Resilience Scale; CI: confidence interval; COPE-28: Brief COPE; DERS: Difficulties in Emotion Regulation Scale; HADS: Hospital Anxiety and Depression Scale; HC: healthy controls; PSWQ: Penn State Worry Questionnaire; STAXI-2: State-Trait Anger Expression Inventory-2; TTS: Takotsubo syndrome.

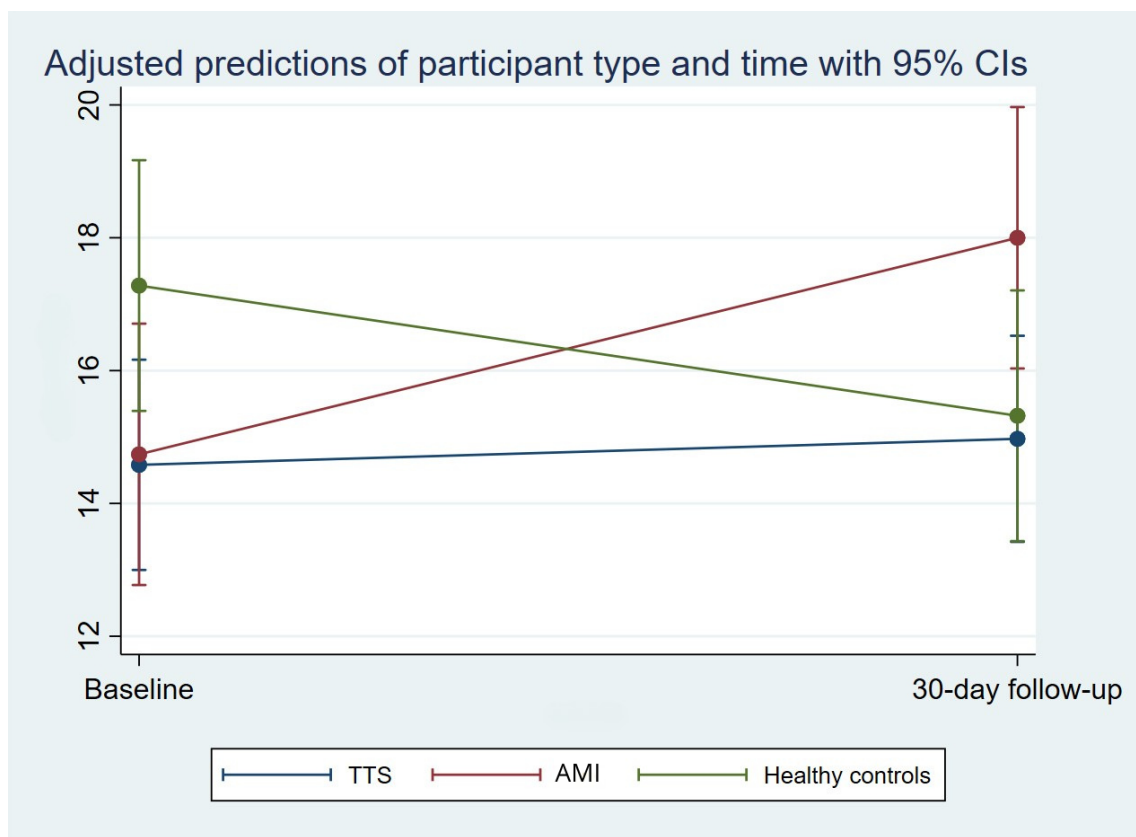


Figure 2. Longitudinal changes in anger-in control (STAXI_CI) in patients with Takotsubo syndrome (TTS), acute myocardial infarction (AMI), and healthy controls. Estimated marginal means of anger-in control at baseline and 30-day follow-up according to study group. Error bars represent 95% confidence intervals.

Abbreviations: AMI: Acute myocardial infarction; CI: Confidence interval; TTS: Takotsubo syndrome.

Brief COPE (COPE-28). For the cognitive coping subscale, patients with AMI showed a decline in cognitive coping over the 30-day follow-up, whereas HC exhibited an increase, and this interaction remained significant in the models adjusting for each covariate separately. No statistically significant effects of time or group $\times$ time interactions were detected for the remaining coping dimensions after adjustment.

Difficulties in Emotion Regulation Scale (DERS). Patients with AMI continued to report lower lack of emotional attention scores than HC after adjustment for age, sex, and smoking status, although this difference was attenuated after adjustment for alcohol consumption. The time effect for this subscale also remained significant after adjustment for age, sex, and alcohol consumption, with HC showing lower scores at the 30-day follow-up, whereas no time $\times$ group interactions were detected. For the emotional confusion subscale, patients with AMI also tended to report lower scores than HC, although this

association remained significant only after adjustment for sex. Conversely, patients with AMI showed higher emotional rejection scores than HC after adjustment for age and sex. Finally, patients with TTS continued to report higher emotional lack of control than HC after adjustment for age and sex, but this difference was attenuated after adjustment for alcohol consumption and smoking status. No consistent adjusted associations were found for emotional life interference or the overall DERS score.

Penn State Worry Questionnaire (PSWQ). Adjustment for potential confounders did not materially modify the primary findings, and no consistent effects of time, group, or time $\times$ group interactions were observed.

In additional multivariable analyses simultaneously adjusting for age, sex, smoking status, and alcohol consumption, the group $\times$ time interaction for anger-in control remained statistically significant ($p = 0.0003$), whereas the interaction for cognitive coping was no longer statistically significant ($p = 0.20$).

Model diagnostics for anger-in control and cognitive coping models showed an overall good approximation of residuals to normality, with only minor deviations at the extremes. Residual-versus-fitted plots showed no concerning systematic patterns. Examination of participant-level estimates did not identify individual observations that warranted exclusion or raised concerns regarding model validity. Similar diagnostic patterns were observed before and after simultaneous covariate adjustment.

4. Discussion

The present study investigated the evolution of psychological characteristics during the first month across patients with TTS, patients with AMI, and HC. Overall, our findings indicate that most psychological outcomes did not show statistically significant longitudinal changes among participants included in the 30-day follow-up analyses during the early recovery period. Notably, anger-in control showed a differential longitudinal trajectory in patients with AMI compared with HC, and this interaction remained significant after correction for multiple testing. An interaction was also observed for cognitive coping in the primary analysis, although this finding did not survive FDR correction and should therefore be considered exploratory.

Although ventricular function generally normalizes within the first weeks after the acute event^{1,2} most psychological characteristics did not show statistically significant longitudinal changes over time. This finding may suggest that the psychological characteristics identified shortly after diagnosis are not entirely explained by a transient emotional reaction to the acute cardiac event.

The dissociation observed between cardiac and psychological recovery may also reflect the marked heterogeneity of TTS. Rather than representing a single disease entity, TTS is increasingly recognized as a heterogeneous condition comprising distinct clinical phenotypes with potentially different pathophysiological mechanisms and clinical outcomes.²³ Consistent with this perspective, latent class analysis has identified distinct TTS phenotypes, reinforcing the concept that patients with TTS do not represent a homogeneous population. Our findings extend this concept by suggesting that psychological functioning may represent an additional dimension of this heterogeneity. Inflammatory pathways may also contribute to the complex pathophysiology underlying cardiovascular disease.²⁴

These results also extend the findings of our previous cross-sectional study¹⁰, in which patients evaluated years after TTS exhibited higher neuroticism and greater

difficulties in emotion regulation than both comparison groups. Although cross-sectional data could not determine whether these characteristics persisted over time, the present longitudinal findings suggest that they are already evident during the early recovery period and did not show statistically significant changes during the first month among participants included in the longitudinal follow-up.

Evidence regarding the longitudinal evolution of psychological functioning after TTS remains scarce. Most previous studies have relied on cross-sectional designs, assessing patients months or years after the acute event, making it difficult to establish whether the observed psychological profile was already present before the acute event or emerged afterwards.⁶ To our knowledge, only Sundelin *et al.*²⁵ have prospectively evaluated psychological outcomes after TTS. However, their study included a relatively small sample, lacked comparison groups, and focused mainly on perceived stress and patients' recovery experiences. Therefore, the present study extends the available evidence by providing longitudinal comparisons of multiple psychological domains.

Anger-in control showed a significant longitudinal interaction between groups, which remained significant after FDR correction and multivariable adjustment. Patients with AMI showed a greater increase in anger-in control scores during follow-up, whereas no statistically significant changes were detected in patients with TTS or HC. One hypothesis that may warrant investigation is that patients with AMI receive clearer information regarding the causes of their condition, available treatments, and secondary prevention strategies, which may contribute to a greater sense of control during recovery. Although exploratory, this finding suggests that psychological adaptation during the first month after an acute cardiac event may differ according to diagnosis. More generally, AMI represents a clinically heterogeneous condition in which prognosis is influenced by comorbidities and therapeutic factors, highlighting the importance of considering the broader clinical context when interpreting psychological trajectories following the acute event.²⁶

An exploratory finding concerned cognitive coping. In the primary analysis, patients with AMI showed a decline in cognitive coping over the 30-day follow-up relative to HC; however, this interaction did not remain statistically significant after FDR correction or multivariable adjustment and should therefore be interpreted cautiously. Within the transactional model of stress and coping proposed by Lazarus and Folkman²⁷, the impact of stress on cardiovascular health depends not only on the intensity of the stressor itself but also on the coping strategies adopted and the social context in which they are deployed.

Consistent with this framework, coping strategies may play an important role in psychological adjustment following acute cardiovascular events. In patients with AMI, less avoidant and more problem-oriented coping strategies have been associated with better quality of life and adaptation after the acute event.²⁸ An alternative hypothesis is that the transition from hospital care to self-management may require patients to cope with greater uncertainty and fewer external sources of support. This change could reduce the use of cognitive strategies aimed at actively reframing or managing stressful experiences.

Among the variables showing between-group differences, patients with TTS exhibited lower resilience than HC across assessments. Resilience has emerged as a positive psychological resource associated with better cardiovascular health and prognosis.^{7,29} Consistent with this, Hahad *et al.*³⁰ reported that individuals with low resilience had a 38% higher likelihood of developing cardiovascular disease and a 36% higher risk of all-cause mortality during follow-up. Although the present study cannot determine whether reduced resilience preceded the onset of TTS or developed as a consequence of the syndrome, these findings suggest that lower resilience did not show statistically significant longitudinal changes during the early recovery period.

Patients with TTS also reported lower anxiety levels than HC throughout the study period. Although this finding was unexpected, it should be interpreted cautiously. Given the observational nature of the study, it is not possible to determine whether this difference reflects pre-existing psychological characteristics, differences in symptom reporting, or factors related to the early post-acute phase. Further longitudinal studies are needed to clarify this finding.

Between-group differences were also observed in specific dimensions of emotion regulation. Patients with AMI reported lower lack of emotional attention than HC throughout the study period. Likewise, patients with AMI showed lower emotional confusion but higher emotional rejection than HC whereas patients with TTS exhibited greater emotional lack of control than HC. Effective emotion regulation depends on recognizing, understanding, accepting, and modulating emotional responses, and impairments in these processes have been associated with poorer psychological adjustment to stressful experiences.^{17,31} One hypothesis is that the acute cardiac event may increase patients' awareness of their internal emotional states, leading to greater attention to emotional experiences. However, greater emotional awareness does not necessarily imply more adaptive emotion regulation, as reflected by the higher emotional rejection scores observed

in patients with AMI. Importantly, because no significant time $\times$ group interactions were observed, these findings should be interpreted as between-group differences observed across assessments rather than evidence of differential longitudinal change.

Sensitivity analyses showed that adjustment for alcohol consumption attenuated several between-group differences. Because alcohol use differed substantially across diagnostic groups and the longitudinal sample was relatively small, it remains unclear whether this attenuation reflects a true confounding effect of alcohol consumption or the reduced statistical power associated with the adjusted models. Importantly, the group $\times$ time interaction for anger-in control remained significant in the multivariable model, whereas the interaction for cognitive coping did not. Together with the FDR-corrected analyses, these findings support anger-in control as the most robust longitudinal finding.

4.1. Limitations and future directions

This study has several limitations. First, the sample size, particularly in the AMI group, was relatively small, which may have limited the statistical power to detect subtle longitudinal changes. In addition, a considerable proportion of participants did not contribute sufficient 30-day data for inclusion in the longitudinal analyses. Follow-up procedures were substantially affected by operational disruptions during the COVID-19 pandemic, and absence of follow-up did not necessarily reflect participant refusal or disengagement. Attrition analyses showed generally small standardized differences in baseline psychological characteristics between participants with sufficient and insufficient/no follow-up data across the three diagnostic groups, although some sociodemographic and clinical differences were observed within the AMI group. However, because the specific reason for missing follow-up was not prospectively recorded at the individual participant level, the missing-at-random assumption cannot be formally established and potential selection bias cannot be completely excluded. Importantly, the mixed-effects approach addresses questionnaire-level missingness among participants included in the longitudinal cohort but does not eliminate potential selection bias associated with absence of follow-up. Therefore, the longitudinal estimates should be interpreted as applying primarily to participants with sufficient follow-up psychological data.

In addition, the completeness and source of baseline clinical information differed across groups. Clinical information for TTS and AMI participants was obtained from medical records, whereas corresponding information for HC was self-reported and substantially less complete

for several variables. This differential ascertainment may have introduced information bias and limits the interpretation of between-group comparisons of baseline clinical characteristics. Furthermore, potentially relevant characteristics of the index event, including TTS subtype, triggering event, ventricular function, hemodynamic severity, intensive care admission, and other markers of acute clinical severity, were not systematically available for the present analyses. As psychological responses may vary according to the severity and circumstances of the index event, residual clinical confounding could not be meaningfully addressed and cannot be excluded. A history of psychological disorders was obtained from available medical records for patients with TTS and AMI and from self-report for HC. However, this information was not based on a systematic psychiatric assessment, and detailed information regarding specific pre-existing psychiatric diagnoses or premorbid psychological functioning was not systematically available. Therefore, the absence of a recorded history of psychological disorders should not necessarily be interpreted as the absence of a pre-existing psychiatric condition.

Second, recruitment procedures may have introduced additional sources of bias. Recruitment center was not included in the adjusted analyses because it was highly confounded with diagnostic group. Specifically, all participants with AMI and all HC were recruited from a single center, whereas participants with TTS were recruited across multiple centers, preventing the independent estimation of center effects. Moreover, HC were recruited using community-based non-probability sampling; therefore, a healthy volunteer effect cannot be excluded. Baseline psychological assessments were also conducted in different settings, with patients evaluated during hospitalization and HC assessed at enrollment, which may have influenced responses to the psychological questionnaires.

Third, follow-up was limited to the first month after the acute event. Although this period is clinically relevant because ventricular recovery usually occurs during these weeks, longer follow-up is needed to determine whether the observed psychological profile persists or changes over time.

Fourth, psychological functioning was assessed exclusively through self-report questionnaires, which may be influenced by response bias. In addition, clinical information for HC was based on self-report because medical records were not available.

Finally, the prospective observational design precludes conclusions regarding the temporal direction of the associations observed, and it remains unclear whether the

psychological characteristics identified preceded the onset of TTS or developed as a consequence of the syndrome.

Despite these limitations, the present study provides one of the first longitudinal evaluations of a broad range of psychological characteristics during the early recovery period after TTS, including both cardiac AMI and HC. These findings suggest that psychological assessment should be incorporated into routine follow-up after TTS. This approach is consistent with recent international expert consensus guidance highlighting the challenges that may persist after TTS recovery and the importance of continued follow-up beyond the acute phase.³² In particular, the routine cardiology review performed approximately 30 days after the acute event may represent an appropriate opportunity for an initial psychological evaluation. Given the absence of statistically detectable changes in most psychological characteristics during the period in which ventricular recovery is typically expected, additional assessments at later stages of recovery, such as six months after the acute event, may help identify patients with persistent emotional difficulties who could benefit from targeted psychological interventions. Such interventions could target emotional awareness, understanding, expression, and regulation.

5. Conclusion

In summary, the present findings indicate that most psychological outcomes did not show statistically significant longitudinal changes among participants included in the 30-day follow-up analyses. Anger-in control showed the most robust differential longitudinal change, with a greater increase among patients with AMI than HC that remained significant after correction for multiple testing and multivariable adjustment. The interaction observed for cognitive coping in the primary analysis did not survive these additional analyses and should therefore be considered exploratory. Although these results cannot determine whether the observed psychological characteristics predated the acute event, they may indicate that such characteristics are not fully explained by the immediate emotional impact of the syndrome. Taken together, these findings suggest that the absence of changes in most psychological outcomes during the first month does not appear to parallel the expected cardiac recovery after TTS. However, these findings should be interpreted in light of the relatively small longitudinal sample and require confirmation in larger prospective studies.

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Conflict of interest

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Ethics approval and consent to participate

The study was conducted in accordance with the ethical

standards of the Declaration of Helsinki (World Medical Association, 2024 revision). The study protocol was approved by the Research Ethics Committee (CEIm) of Hospital Universitario 12 de Octubre (CEIm No. 17/384; approval date: December 19, 2017). This multicenter ethical approval covered all nine participating centers included in the Tako-Tsubo Brain Project. All participants provided written informed consent.

Consent for publication

Not applicable.

Availability of data

The datasets generated and analyzed during the current study are not publicly available due to the sensitive nature of the questions asked in this study but are available from the corresponding author upon reasonable request.

Further disclosure

Generative artificial intelligence was used to assist with English language editing. All AI-assisted text was reviewed and approved by the authors, who take full responsibility for the final content.

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