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Cardiac troponin elevation and mortality in takotsubo syndrome: New insights from the international takotsubo registry

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Abstract

Background: The clinical relevance of cardiac troponin (cTn) elevation in takotsubo syndrome (TTS) remains uncertain. The present study sought to investigate the role of cardiac troponin (cTn) elevations in mortality prediction of patients with Takotsubo syndrome (TTS).

Methods: Patients enrolled in the International Takotsubo (InterTAK) Registry from January 2011 to February 2020 with available data on peak cTn levels were included in the analysis. Peak cTn levels during the index hospitalization were used to define clinically relevant myocardial injury. The threshold at which clinically relevant myocardial injury drives mortality at 1 year was identified using restricted cubic spline analysis.

Results: Out of 2′938 patients, 222 (7.6%) patients died during 1-year follow-up. A more than 28.8-fold increase of cTn above the upper reference limit was identified as threshold for clinically relevant myocardial injury. The presence of clinically relevant myocardial injury was significantly associated with an increased risk of mortality at 5 years (adjusted HR 1.58, 95% CI 1.18–2.12, $p = .002$). Clinically relevant myocardial injury was related to an increased 5-year mortality risk in patients with apical TTS (adjusted HR 1.57, 95% CI 1.21–2.03, $p = .001$), in presence of physical stressors (adjusted HR 1.60, 95% CI 1.22–2.11, $p = .001$), and in absence of emotional stressors (adjusted HR 1.49, 95% CI, 1.17–1.89, $p = .001$).

Conclusion: This study for the first time determined a troponin threshold for the identification of TTS patients at excess risk of mortality. These findings advance risk stratification in TTS and assist in identifying patients in need for close monitoring and follow-up.

KEYWORDS
myocardial injury, risk prediction, takotsubo syndrome, troponin

1 | INTRODUCTION

Takotsubo syndrome (TTS), predominantly affecting postmenopausal women, represents an acute heart failure syndrome characterized by left ventricular wall motion abnormalities and elevated cardiac biomarkers.[1–3] Variable clinical presentations, along with occurrence in younger patients and men, have been described.[4–6] Given the wide spectrum of clinical presentations and the serious complications related to severe courses of TTS, early risk prediction and identification of patients at excess risk of adverse events is important.[7]

Elevated cardiac troponin (cTn) levels represent a marker for myocardial injury and ischemia in different clinical scenarios, extending beyond acute myocardial infarction. These include conditions such as tachyarrhythmias, heart failure, myocarditis, pulmonary embolism, and TTS.[8,9] A transient increase in cTn levels, along with a distinct cardiac biomarker pattern, is typically observed in TTS patients.[1,10] Notably, cTn levels at

admission are often similar in TTS and acute myocardial infarction, although peak values are generally lower in TTS.[1,10] While the clinical relevance of postprocedural myocardial injury or infarction has extensively been investigated in patients with coronary artery or structural heart disease undergoing transcatheter procedures,[11–17] the role of cTn in the risk stratification of TTS patients remains uncertain and threshold values have not yet been investigated.

The aim of the present study was to identify a cTn threshold associated with higher risk of mortality, using data from the large, multicenter International Takotsubo (InterTAK) Registry.

2 | METHODS

2.1 | Study population

The study is based on data from the InterTAK Registry (www.takotsubo-registry.com, NCT01947621).[6,10,18] Patients diagnosed with TTS were enrolled in the registry from January 2011 to February 2020 at 50 centers in 15 countries. Diagnosis of TTS was based on the InterTAK Diagnostic Criteria.[1] Patients were treated according to current guidelines and obtained optimal medical management.[19] In all patients demographic, clinical, laboratory, ECG, echocardiography, and cardiac catheterization data, along with information on in-hospital complications and long-term follow-up were collected. Follow-up was performed by either clinical visits, phone calls, or medical records.

The study was conducted in full conformance with the principles of the Declaration of Helsinki and was approved by the institutional review boards of the participating centers and the respective local ethics committees. Due to the partly retrospective study design, ethics committees of most sites waived the need for informed consent. When informed consent was requested or when patients were included prospectively, written informed consent was obtained from patients.

2.2 | Definition of clinically relevant myocardial injury

Peak cTn levels (including troponin T, troponin I, and high-sensitivity troponin T) during the index hospitalization were used to define clinically relevant myocardial injury. The threshold at which clinically relevant myocardial injury drives mortality at 1 year was identified using restricted cubic spline analysis. The lower 95% confidence interval (CI) was used to determine the ideal cutoff value for the fold increase of peak cTn levels above the URL.

All laboratory analyses were performed according to local standard operating procedures, and baseline and peak values were collected in the database. cTn levels were measured as part of the routinely performed laboratory analyses and were described as multiples of their upper reference limits (URL) to allow for standardization of measurements.

2.3 | Statistical analysis

Continuous variables are presented as mean and standard deviation (SD) and categorical variables as numbers and percentages. Continuous variables were compared using the Mann–Whitney-*U* test and categorical variables using chi-square tests for proportion. First, univariable Cox regression models were used to investigate the association of peak cTn levels with mortality at 1 year. Second, nonparametric restricted cubic splines were used to model the association of the fold increase of peak cTn levels above the URL with mortality at 1 year. The definition of clinically relevant myocardial injury was based on rates of mortality at 1 year. Shorter time intervals would limit the statistical power of the analysis and longer time intervals would potentially increase the effect of confounding factors. Models with different numbers of knots (3, 4, and 5 knots) were compared. As the model with three knots showed the best performance based on the Akaike information criterion (AIC), a model with three flexible knots was compared with a model where the knots were placed at tertiles of the variable. The final model with three flexible knots was again determined using the AIC. The lower 95% confidence interval (CI) was used to determine the ideal cutoff value for the fold increase of peak cTn levels above the URL and the cohort was stratified based on the determined cutoff value. In addition, sensitivity analyses were performed to assess the robustness of the retrieved cutoff value. Kaplan–Meier analysis and univariable and multivariable Cox regression analyses were used to compare mortality rates among groups (above versus below the cutoff value). Models were adjusted for baseline variables significantly ($p < .05$) related to mortality at 5 years (age, sex, body mass index, chronic obstructive pulmonary disease, atrial fibrillation, diabetes, dyslipidemia, presence of emotional stressors, and presence of physical stressors). MACCE were defined as a composite of mortality, myocardial infarction, recurrence of TTS, stroke, and transient ischemic attack. Findings were considered statistically significant at the 0.05 level. Statistical analyses were performed with R software for statistical computing

(Version 4.0.2) and SPSS (Version 27, IBM Corp., Armonk, NY, USA).

3 | RESULTS

3.1 | Definition of a threshold for clinically relevant myocardial injury

Out of a total 3′531 TTS patients, 2′938 (83.2%) patients with available data on peak cTn levels were included in the present analysis. Of these, 222 (7.6%) patients died during the 1-year follow-up. A significant association between peak cTn levels and mortality at 1 year was observed in univariable Cox regression analysis (HR 1.01, 95% CI 1.00–1.02, $p < .001$). Restricted cubic splines with four knots placed at flexible locations were then used to model the relation of peak cTn levels above the URL with mortality at 1 year (Figure 1). At a 28.8-fold increase of peak cTn levels above the URL, the lower end of the CI crossed a relative risk for all-cause mortality of 1. A ≥ 28.8-fold increase of peak cTn levels above the URL was therefore defined as clinically relevant myocardial injury. The lower end of the CI crossed a relative risk for all-cause mortality of 1 at a 35.5-fold increase of peak cTn levels above the URL in women and at a 166.5-fold increase in men, respectively.

Kaplan–Meier analyses showed that mortality at 1 year was significantly higher in patients with peak cTn levels ≥28.8-fold above the URL than in those with values below (Log Rank $p < .001$, Figure 2). Sensitivity analyses testing the robustness of the threshold are given in Table S1. The estimated threshold remained unchanged when restricting the univariable analysis follow-up time to 30 days and 5 years and was similar when testing for rates of MACCE.

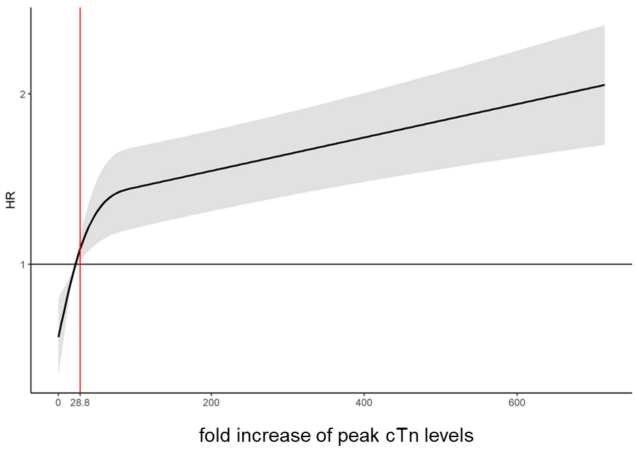

FIGURE 1 Restricted cubic spline analysis to determine the threshold at which myocardial injury drives mortality in patients with Takotsubo syndrome. The relative risk of mortality according to the degree of peak cTn elevation above the URL is shown. Grey areas represent the 95% confidence interval. cTn = cardiac troponin, URL = upper reference limit.

3.2 | Baseline characteristics

Mean peak cTn level above the URL was 18.0 (6.1–46.1)-fold. Clinically relevant myocardial injury as defined by a ≥ 28.8-fold increase of peak cTn levels occurred in 1104 (37.6%) patients. Baseline characteristics according to the presence/absence of clinically relevant myocardial injury are given in Table 1. Patients with clinically relevant myocardial injury were more often men, less frequently active smokers, more frequently presented with the apical TTS type, and less often reported dyspnea as the initial symptom. They less often had chronic obstructive pulmonary disease, but more often presented with lower blood pressure and increased left ventricular end-diastolic pressure and were more likely to present with ST-segment elevation and cardiogenic shock in need for catecholamines and mechanical circulatory support. Patients with clinically relevant myocardial injury had increased baseline and peak creatine kinase and C-reactive protein levels. They more often underwent percutaneous coronary intervention for concomitant coronary artery disease.

3.3 | Clinically relevant myocardial injury and mortality

All-cause mortality of patients with and without clinically relevant myocardial injury is given in Table 2. The presence of clinically relevant myocardial injury was significantly associated with an increased risk of mortality at 30 days (HR 1.68, 95% CI 1.22–2.34, $p = .002$), at 1 year (HR 1.57, 95% CI 1.21–2.05, $p = .001$), and at 5 years (HR 1.50, 95% CI 1.20–1.88, $p < .001$). The associations remained significant after multivariable adjustments for age, sex, body mass index, chronic obstructive pulmonary disease, atrial fibrillation, diabetes, dyslipidemia, presence of emotional stressors, and presence of physical stressors (Table 3). When cardiogenic shock at presentation was included in the multivariable model, the associations of clinically relevant myocardial injury with 5-year mortality remained significant (adjusted HR 1.37, 95% CI 1.02–1.85, $p = .04$). Clinically relevant myocardial injury was not related to the risk of mortality at 5 years in a landmark analysis including events between 30 days and 5 years (HR 1.38, 95% CI 0.98–1.85, $p = .07$).

The association of clinically relevant myocardial injury with 5-year mortality was significant in patients with apical TTS (adjusted HR 1.57, 95% CI 1.21–2.03, $p = .001$), but not in those with non-apical forms (adjusted HR 1.25, 95% CI 0.78–2.00, $p = .36$, Figure 3). Further, the association of

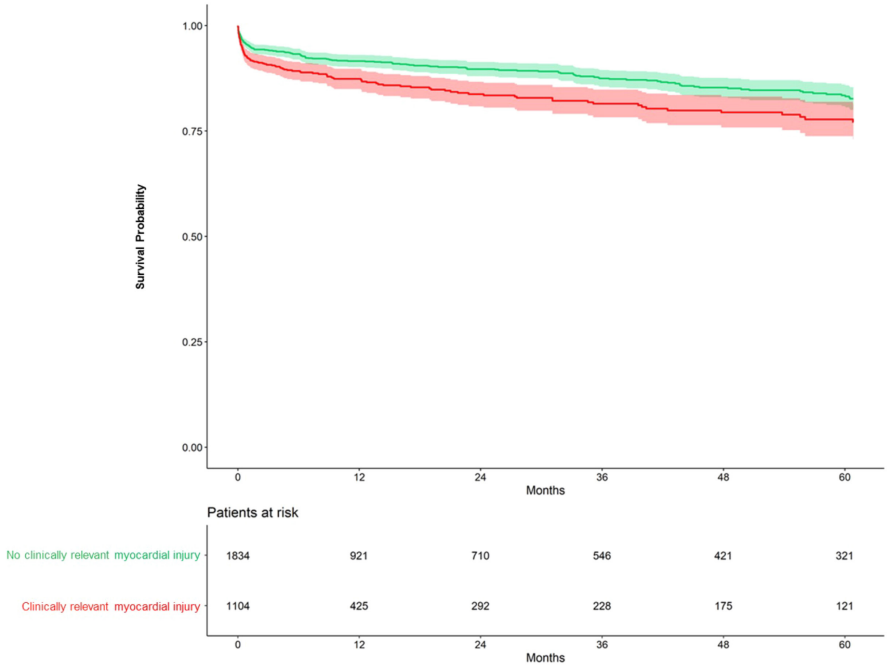

FIGURE 2 Kaplan–Meier estimates of survival according to the presence/absence of clinically relevant myocardial injury in patients with Takotsubo syndrome.

clinically relevant myocardial injury with 5-year mortality was significant in patients with physical stressors (adjusted HR 1.60, 95% CI 1.22–2.11, $p=.001$) and in those with absence of emotional stressors (adjusted HR 1.49, 95% CI, 1.17–1.89, $p=.001$, Figure 4). The association of clinically relevant myocardial injury with 5-year mortality was not statistically significant in patients with antidepressants on admission (adjusted HR 1.49, 95% CI 0.54–4.16, $p=.44$).

4 | DISCUSSION

This study determined the prognostic value of acute myocardial injury as defined by peak cTn levels in TTS patients. Based on cubic spline analysis, a 29-fold increase in peak cTn levels defined clinically relevant myocardial injury in TTS patients. A strong association between clinically relevant myocardial injury and mortality was observed in patients with the apical form of TTS, those with physical stressors, and those with absence of emotional stressors. The proposed new definition of clinically relevant myocardial injury assists in the identification of TTS patients at excess risk of adverse events, and peak cTn levels should be therefore considered in the setting of risk stratification of TTS patients.

4.1 | Clinically relevant myocardial injury in TTS

Levels of cTn are only moderately elevated in most TTS patients and typically lower than those seen in patients with acute myocardial infarction, despite the presence of extensive left ventricular wall motion abnormalities.[10,20,21] Data on the clinical relevance of cardiac biomarker elevations in TTS patients are scarce, and most studies are limited by their small sample size and short-term follow-up.[10] Based on the presence of clinically relevant myocardial injury, a third of TTS patients were identified as patients with an increased risk of mortality and such patients may represent a particularly vulnerable patient subset in need for close monitoring and follow-up. Patients with clinically relevant myocardial injury were more likely men, less frequently active smokers, more frequently presented with the apical TTS type, and less often reported dyspnea as the initial symptom. They more often had lower blood pressure and increased left ventricular end-diastolic pressure, and were more likely to present with ST-segment elevation and cardiogenic shock in need of catecholamines and mechanical circulatory support. Patients with clinically relevant myocardial injury had increased baseline and peak creatine kinase and C-reactive protein levels. The higher cutoff value for cTn levels identified in men as compared to women is in line with previous studies showing higher cTn levels in men with TTS.[22]

While pathophysiological mechanisms underlying myocardial damage in coronary artery and structural heart disease have extensively been studied, processes contributing to cTn elevations in TTS patients, irrespective of the presence of concomitant coronary artery disease, are only incompletely understood. Epicardial multivessel spasm and coronary microvascular dysfunction are considered to principally contribute to transient myocardial stunning and cardiac biomarker release in

TABLE 1 Baseline characteristics according to the presence of clinically relevant myocardial injury defined as a 28.8-fold increase of peak cardiac troponin levels above the upper reference limit.

Variables	Total $N = 2938$	Myocardial injury $N = 1104$	No myocardial injury $N = 1834$	p-value
Clinical data				
Age	68.0 ± 12.4	68.5 ± 12.8	67.7 ± 12.1	.13
Women	2602 (88.6%)	961 (87.0%)	1641 (89.5%)	.048
BMI	24.7 (5.3%)	24.6 (5.1%)	24.8 (5.4%)	.30
Takotsubo type				
Apical	2085 (71.0%)	815 (73.8%)	1270 (69.2%)	.008
Midventricular	676 (23.0)	237 (21.5%)	439 (23.9%)	.12
Basal	49 (1.7%)	20 (1.8%)	29 (1.6%)	.64
Focal	128 (4.4%)	32 (2.9%)	96 (5.2%)	.003
Stressors				
Emotional	815 (27.7%)	284 (25.7%)	531 (29.0%)	.058
Physical	1217 (41.4%)	471 (42.7%)	746 (40.7%)	.29
Emotional and physical	166 (5.7%)	62 (5.6%)	104 (5.7%)	.95
Symptoms				
Chest pain	1848 (68.0%)	696 (68.7%)	1152 (67.6%)	.54
Dyspnea	1210 (44.6%)	418 (41.2%)	792 (46.6%)	.006
Syncope	266 (9.6%)	105 (10.2%)	161 (9.3%)	.43
Systolic blood pressure	130.4 ± 29.2	127.5 ± 29.5	132.2 ± 28.9	<.001
Diastolic blood pressure	76.7 ± 17.1	75.5 ± 17.0	77.5 ± 17.2	.006
ECG changes				
ST segment elevation	1179 (43.8%)	508 (50.1%)	671 (40.0%)	<.001
ST segment depression	232 (8.8%)	86 (8.8%)	146 (8.8%)	.99
T-wave inversion	1143 (43.6%)	371 (38.1%)	772 (46.9%)	<.001
LVEDP	21.8 ± 8.0	23.1 ± 7.6	21.2 ± 8.2	<.001
Diabetes	454 (15.6%)	153 (14.0%)	301 (16.5%)	.08
Hypertension	1836 (63.2%)	667 (61.4%)	1169 (64.3%)	.12
Dyslipidemia	929 (32.4%)	355 (32.9%)	574 (32.0%)	.62
Smoking	502 (20.7%)	170 (18.5%)	332 (22.1%)	.03
COPD	338 (11.8%)	94 (8.8%)	244 (13.5%)	<.001
Atrial fibrillation	180 (6.7%)	63 (6.2%)	117 (7.0%)	.45
Coexisting coronary artery disease	417 (21.8%)	168 (22.0%)	249 (21.7%)	.86
Cardiogenic shock	287 (9.8%)	131 (11.9%)	156 (8.6%)	.003
Use of catecholamines	362 (12.4%)	156 (14.2%)	206 (11.3%)	.02
Mechanical circulatory support	79 (2.8%)	44 (4.2%)	35 (2.0%)	<.001
Mechanical ventilation	524 (17.9%)	213 (19.4%)	311 (17.0%)	.11
Resuscitation	215 (7.3%)	76 (6.9%)	139 (7.6%)	.49
PCI during index procedure	74 (3.9%)	38 (5.0%)	36 (3.2%)	.046
Laboratory data				
Baseline cTn (x URL)	33.1 ± 102.2	8.1 ± 7.7	74.3 ± 157.7	<.001
Peak cTn (x URL)	47.7 ± 144.6	10.3 ± 8.0	110.0 ± 222.2	–
Baseline CK (x URL)	1.8 ± 4.6	2.4 ± 5.8	1.4 ± 3.7	<.001
Peak CK (x URL)	2.4 ± 5.6	3.3 ± 7.0	1.8 ± 4.6	<.001

TABLE 1 (Continued)

Variables	Total $N = 2938$	Myocardial injury $N = 1104$	No myocardial injury $N = 1834$	*p*-value
Baseline BNP (x URL)	21.3 ± 40.7	21.3 ± 42.7	21.3 ± 39.2	.99
Peak BNP (x URL)	25.6 ± 45.2	27.5 ± 50.3	24.3 ± 41.2	.20
Baseline white blood cell count	10.8 ± 5.0	11.3 ± 5.4	10.4 ± 4.8	<.001
Peak white blood cell count	11.9 ± 5.9	12.5 ± 6.3	11.5 ± 5.6	<.001
Baseline CRP (mg/l)	16.9 ± 39.5	19.0 ± 47.2	15.6 ± 34.1	.07
Peak CRP (mg/l)	36.7 ± 63.2	42.5 ± 71.7	33.3 ± 57.3	.001

Note: Values are given as mean and standard deviation or numbers and percentages.

Abbreviations: BMI, body mass index, BNP, brain natriuretic peptide, CK, creatine kinase, COPD, chronic obstructive pulmonary disease, CRP, C-reactive protein, cTn, cardiac troponin, ECG, electrocardiogram, LVEDP, left ventricular end-diastolic pressure, PCI, Percutaneous coronary intervention.

TABLE 2 Outcomes according to presence/absence of clinically relevant myocardial injury as defined by a 28.8-fold increase above the upper reference limit.

Outcome	Myocardial injury	No myocardial injury	Hazard Ratio (95% CI)	*p* value	Adjusted Hazard Ratio (95% CI)	*p* value
All-cause mortality						
At 30 days	71 (6.4)	74 (4.0)	1.68 (1.22–2.34)	.002	1.68 (1.09–2.65)	.02
At 1 year	102 (9.2)	120 (6.5)	1.57 (1.21–2.05)	0001	1.62 (1.14–2.29)	.007
At 5 years	132 (12.0)	175 (9.5)	1.50 (1.20–1.88)	<.001	1.58 (1.18–2.12)	.002
Landmark analysis (between 30 days and 5 years)			1.34 (0.98–1.85)	.07		

Note: Reported are numbers of first events (%), hazard ratios with corresponding 95% confidence intervals (CI) from Cox regression models. Multivariable Cox regression models were adjusted for age, sex, body mass index, COPD, atrial fibrillation, diabetes, dyslipidemia, presence of emotional stressors, and presence of physical stressors.

TTS.[1,23,24] Increased left ventricular wall tension due to left ventricular dysfunction as well as hypotension when left ventricular failure occurs may further aggravate myocardial oxygen supply–demand mismatch in more severe cases.[1] The hypothesis of catecholamine toxicity is supported by endomyocardial biopsy findings of contraction band necrosis in TTS patients and animal models of acute heart failure.[1,20,25,26]

4.2 | Clinically relevant myocardial injury and outcomes in TTS

Elevated cTn levels have previously been linked with adverse in-hospital events in TTS patients.[10] This analysis extends these findings to long-term mortality data and defines a threshold cTn value for a new definition of clinically relevant myocardial injury in TTS. Mortality at 30 days, 1 year, and 5 years was significantly higher in patients with as compared to those without clinically relevant myocardial injury, and associations remained significant after multivariable adjustment. As clinically relevant myocardial injury was not related to the risk of mortality in a landmark analysis including events between 30 days and 5 years, cardiac biomarker release may predominantly reflect an increased risk of early rather than late mortality after a TTS event. Future studies are needed to investigate the potential of cardiac biomarker-guided patient management in TTS and whether acute measures to reduce the amount of myocardial injury may improve prognosis.

The association of clinically relevant myocardial injury with mortality was significant in patients with the apical form of TTS, but not in those with non-apical forms. Further, the association of clinically relevant myocardial injury with mortality was significant in patients with physical stressors, and in those with absence of emotional stressors. Pathophysiological mechanisms underlying the observed associations in different subgroups of patients remain to be further elucidated.

Variable	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age (years)	1.02 (1.01–1.03)	<.001	1.01 (1.00–1.02)	.002
Female sex	0.48 (0.37–0.64)	<.001	0.74 (0.51–1.07	.11
Body mass index	0.96 (0.93–0.99)	.004	0.95 (0.93–0.98)	.002
Apical form	1.25 (0.97–1.62)	.09		
Midventricular form	0.92 (0.70–1.20)	.53		
Basal form	0.54 (0.17–1.68)	.29		
Physical stressor	3.55 (2.79–4.51)	<.001	2.62 (1.85–3.73)	<.001
Emotional stressor	0.22 (0.15–0.33)	<.001	0.38 (0.21–0.70)	.002
Hypertension	0.87 (0.69–1.09)	.22		
Diabetes	1.83 (1.41–2.38)	<.001	2.04 (1.45–2.89)	<.001
Dyslipidemia	0.74 (0.58–0.97)	.03	0.89 (0.65–1.21)	.45
COPD	1.45 (1.06–1.98)	.02	1.23 (0.84–1.81)	.28
Atrial fibrillation	2.58 (1.85–3.59	<.001	2.49 (1.66–3.75)	<.001
Clinically relevant myocardial injury	1.50 (1.20–1.88)	<.001	1.58 (1.18–2.12)	.002

All variables with significance level <0.05 were included in the multivariable model.

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease, HR, hazard ratio.

TABLE 3 Univariable and multivariable predictors of 5-year mortality.

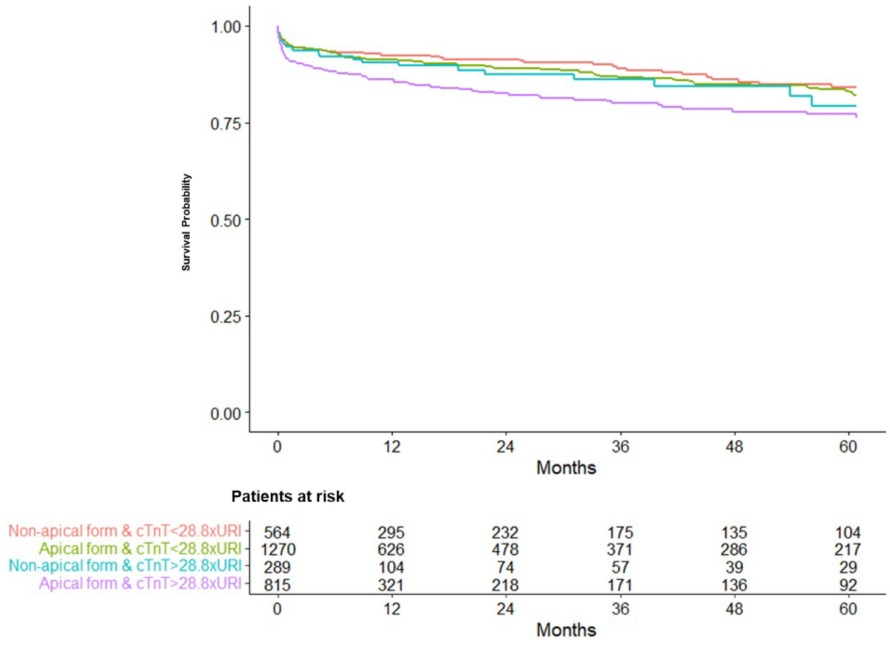

FIGURE 3 Kaplan–Meier estimates of survival according to the presence/absence of clinically relevant myocardial injury stratified for the presence/absence of the apical form of Takotsubo syndrome.

4.3 | Limitations

Some limitations merit consideration. This observational study enrolled patients from the largest contemporary cohort of TTS patients among Europe, Australia, Asia, and the United States with available long-term follow-up and mortality data. Although established risk factors were incorporated into the multivariable models, we cannot exclude that unmeasured or unknown confounding factors may have affected the observed associations of cTn levels with outcomes in TTS patients. This study was focusing on mortality as an end point, and future studies are needed to investigate the association of cTn levels with the incidence of heart failure as another important end point in patients suffering from myocardial injury. Also, the cause of death was not captured in the registry and analyses on different causes of death were therefore not possible.

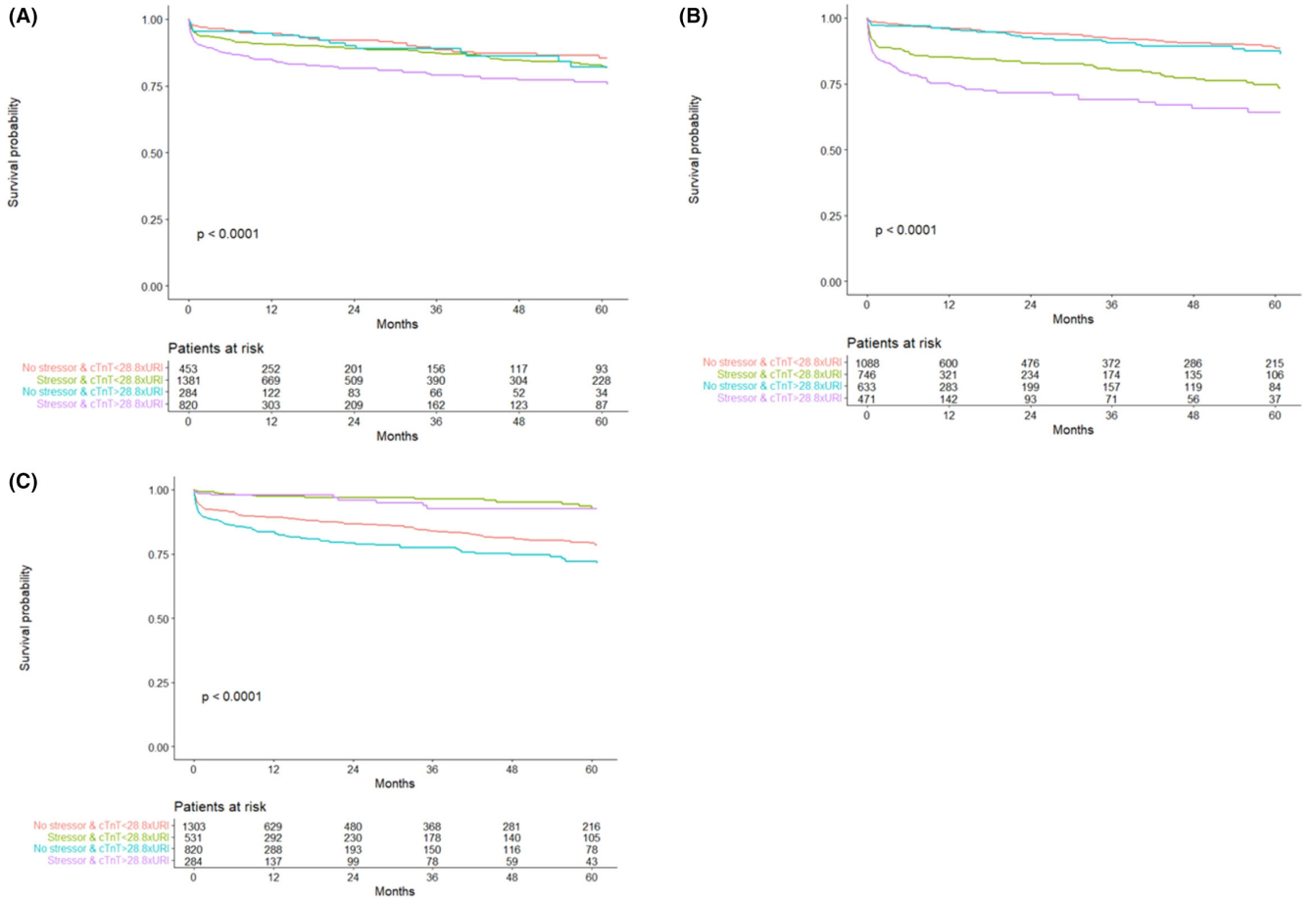

FIGURE 4 Kaplan–Meier estimates of survival according to the presence/absence of clinically relevant myocardial injury stratified for the presence/absence of physical or emotional stressors. (A) Kaplan–Meier estimates of survival in patients with and without clinically relevant myocardial injury stratified according to the presence/absence of physical and/or emotional stressors. (B) Kaplan–Meier estimates of survival in patients with and without clinically relevant myocardial injury stratified according to the presence/absence of physical stressors. (C) Kaplan–Meier estimates of survival in patients with and without clinically relevant myocardial injury stratified according to the presence/absence of emotional stressors.

5 | CONCLUSION

This study for the first time determined a cTn threshold for the definition of clinically relevant myocardial injury in TTS. A 29-fold increase in cTn levels was identified as most appropriate for the identification of TTS patients at excess risk of mortality. Hence, cTn levels should be incorporated into the risk stratification of TTS patients and may assist in the identification of patients in need for close monitoring and follow-up.

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CONFLICT OF INTEREST STATEMENT

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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