Age related differences and outcome of patients with Takotsubo syndrome

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Abstract

Background  Takotsubo syndrome (TS) is an important cardiac disease that affects predominantly postmenopausal women. This study was conducted to determine the impact of age on the short- and long-term outcome of TS patients. Methods & Results  The data from a collective of 114 TS patients with a mean follow-up of 1591 ± 1079 days was retrospectively analysed. The study population was divided into two groups (≤ 65 and > 65 years) so as to evaluate the impact of age on the short- and long-term mortality of TS patients. In-hospital events like life-threatening arrhythmias (14.58% vs. 9.09%; P = 0.036), need for mechanical respiratory support (41.66% vs. 28.78%; P = 0.15) as well as inotropic agent use (22.91% vs. 15.15%; P = 0.29), although not reaching the statistical cut-off, tended to occur more often in the younger group. Heart failure was more common in the elderly age group (P = 0.03). The use of multivariate analysis ruled out age as a significant marker of long term mortality (HR: 1.0; 95% CI: 0.9–1.0; P = 0.60).

Conclusions  Age does not influence the clinical course of TS in terms of the short- as well as long-term outcome. The study revealed a higher incidence of life threatening arrhythmias in the younger patient age-group and a higher incidence of heart failure among the older group of patients.

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Keywords: Age; Cardiovascular risk; Mortality; Takotsubo syndrome

1 Introduction

Takotsubo syndrome (TS), first described in 1990, is a transient disorder of ventricular wall dysfunction characterized by a range of wall motion abnormalities.[1,2] The syndrome affects predominantly elderly postmenopausal women and is often triggered by emotional or physical stress.[3] This kind of cardiomyopathy usually presents itself with symptoms similar to those of acute coronary syndrome (ACS),[4] and is associated with severe clinical complications, such as acute heart failure, malignant arrhythmias, atrial fibrillation, thrombo-embolic events, left ventricular outflow obstruction, mitral valve regurgitation and cardiac rupture.[5–8]

The definitive pathophysiological mechanisms contributing to this form of selective wall-motion abnormality are still unknown, however, it has been hypothesized that sympathetic stimulation due to catecholamine excess, as in the event of an emotionally stressful trigger could play a significant role.[9] The effect of metabolic disturbances, coronary microvascular impairment and multi-vessel epicardial coronary spasm are some of the theories postulated to explain the underlying mechanisms in TS, but these have not been well-established.[10]

There is also relatively poor clarity concerning other significant aspects of the syndrome. For example, it is unclear as to why the elderly generation is especially predisposed to develop TS, and if an age difference could play a role in the follow-up and outcome. Many studies have described the prevalence of TS in the elderly population and researched the impact of age on in-hospital outcome,[11–13] however, the impact of age on the long-term outcome, which was addressed in this study, has not been well-researched.

2 Methods

2.1 Study population

For this analysis, we identified 114 consecutive patients in our institution, diagnosed with TS between January 2003 and September 2015. All patients underwent diagnostic eva-
luation during acute presentation, including electrocardiography, blood sample analysis, echocardiography and coronary angiography. The diagnosis of TS was based on the Mayo clinic criteria, outlined as follows: (1) transient hypokinesia, akinesia, or dyskinesia in the left ventricular mid segments with or without apical involvement; regional wall motion abnormalities that extend beyond a single epicardial vascular distribution; and frequently, but not always, in the event of a stressful trigger; (2) the absence of obstructive coronary disease or angiographic evidence of acute plaque rupture; (3) new ECG abnormalities (ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin; and (4) the absence of pheochromocytoma and myocarditis.[14,15]

The patient cohort was divided into two groups according to age, with the first group including all TS patients ≤ 65 years, and the second constituting TS patients older than 65 years.

A coronary angiography and/or follow-up echocardiography was not performed in a total of 18 patients, leading to age, with the first group including all TS patients ≤ 65 years, and the second constituting TS patients older than 65 years.

The in-hospital outcome data and TS-related complications are summarized in Table 2. In-hospital death occurred in 7.7% and the median in-hospital stay was three days (0–52). Ten patients suffered from cardiogenic shock (15.1%) and 11.6% required inotropic support. Severe complications included life threatening arrhythmias (14.58% vs. 9.09%; P = 0.36), as well as clinical situations demanding need for mechanical respiratory support (41.66% vs. 28.78%; P = 0.15) or use of inotropic agents (22.91% vs. 15.15%; P = 0.29). Nevertheless, data showed that these results were not statistically significant.

### 3 Results

#### 3.1 Demographic characteristics

A total of 114 patients with a mean follow-up of 1591 ± 1079 days were analysed. The mean age was 67.1 years and 83.3% of the patients were female. An emotional trigger was identified in 26.3% and a physical trigger in 56% of the patients (Table 1). There were no significant differences in gender, stress factors and presenting symptoms between both groups.

The evaluation of the medical history, cardiovascular risk factors and relevant cardiovascular diseases showed that the older group suffered atrial fibrillation (30.30% vs. 2.08%; P < 0.01) more often, while smoking was more common in the younger group (26% vs. 10%; P < 0.01). The drugs on admission as well as laboratory parameters were similar in both groups without any significant differences.

Echocardiographic evaluation revealed that apical ballooning and mitral regurgitation were more common in the elderly cohort (both P < 0.01).

#### 3.2 In-hospital outcome

The in-hospital outcome data and TS-related complications are summarized in Table 2. In-hospital death occurred in 7.7% and the median in-hospital stay was three days (0–52). Ten patients suffered from cardiogenic shock (15.1%) and 11.6% required inotropic support. Severe complications included life threatening arrhythmias (14.58% vs. 9.09%; P = 0.36), as well as clinical situations demanding need for mechanical respiratory support (41.66% vs. 28.78%; P = 0.15) or use of inotropic agents (22.91% vs. 15.15%; P = 0.29). Nevertheless, data showed that these results were not statistically significant.
| Variables                        | All patients (n =114) | ≤ 65 yrs (n = 48) | > 65 yrs (n = 66) | *P value |
|---------------------------------|-----------------------|------------------|------------------|-----------|
| **Demographics**                |                       |                  |                  |           |
| Female                          | 95 (83.33%)           | 38 (79.16%)      | 57 (86.36%)      | 0.30      |
| **Symptoms**                    |                       |                  |                  |           |
| Dyspnoe                         | 43 (37.71%)           | 19 (39.58%)      | 24 (36.36%)      | 0.72      |
| Chest pain                      | 58 (50.87%)           | 22 (45.83%)      | 36 (54.54%)      | 0.35      |
| **Clinic parameter**            |                       |                  |                  |           |
| Systolic BP, mmHg               | 131.36 ± 32.18        | 121.02 ± 33.39   | 139.89 ± 28.73   | <0.01     |
| Diastolic BP, mmHg              | 76.64 ± 17.61         | 71.07 ± 20.88    | 80.45 ± 14.02    | 0.02      |
| Heart rate, beats/min           | 100.62 ± 27.15        | 103.5 ± 28.3     | 98.2 ± 26.1      | 0.32      |
| **ECG data**                    |                       |                  |                  |           |
| ST-segment elevation            | 34 (29.82%)           | 12 (25.00%)      | 22 (33.33%)      | 0.33      |
| Inversed T-waves               | 102 (89.47%)          | 44 (91.66%)      | 58 (87.87%)      | 0.03      |
| PQ-interval, ms                  | 160.53 ± 29.41        | 154.83 ± 23.74   | 165.69 ± 32.65   | 0.06      |
| QTc, ms                          | 478.93 ± 52.24        | 466.94 ± 32.88   | 488.66 ± 62.39   | 0.03      |
| **Stress factor**               |                       |                  |                  |           |
| Emotional stress                | 30 (26.31%)           | 12 (25.00%)      | 18 (27.27%)      | 0.78      |
| Physical stress                 | 64 (56.14%)           | 27 (56.25%)      | 37 (56.06%)      | 0.98      |
| None                            | 25 (21.9%)            | 12 (25.00%)      | 13 (19.69%)      | 0.49      |
| **Laboratory values**           |                       |                  |                  |           |
| Troponin I, U/L                 | 3.75 ± 5.38           | 3.20 ± 4.65      | 4.14 ± 5.85      | 0.37      |
| Creatine phosphokinase, U/L     | 651.84 ± 2644         | 933.28 ± 3909.39 | 446.35 ± 993.63  | 0.34      |
| CKMB                            | 36.42 ± 60.33         | 36.89 ± 74.39    | 35.93 ± 42.55    | 0.95      |
| C-reactive protein, mg/L        | 49.44 ± 79.63         | 42.47 ± 70.25    | 54.88 ± 86.44    | 0.43      |
| Hemoglobin, g/dL                | 12.13 ± 2.00          | 12.51 ± 2.33     | 11.86 ± 1.68     | 0.09      |
| Creatinine, mg/dL               | 1.15 ± 0.71           | 1.04 ± 0.45      | 1.24 ± 0.85      | 0.15      |
| **Echocardiography data**       |                       |                  |                  |           |
| LVEF %                          | 38.37% ± 9.42%        | 37.48% ± 11.09%  | 39.05% ± 8.07%   | 0.38      |
| Apical ballooning               | 82 (71.92%)           | 26 (54.16%)      | 56 (84.84%)      | <0.01     |
| Mitral regurgitation            | 60 (52.63%)           | 15 (31.25%)      | 45 (68.18%)      | <0.01     |
| Tricuspid regurgitation         | 49 (42.98%)           | 47 (41.22%)      | 34 (51.51%)      | 0.03      |
| **Medical history**             |                       |                  |                  |           |
| Smoking                         | 36 (31.57%)           | 26 (54.16%)      | 10 (15.15%)      | <0.01     |
| Diabetes mellitus               | 26 (22.80%)           | 9 (18.75%)       | 17 (25.75%)      | 0.37      |
| BMI > 25 kg/m²                  | 31 (27.19%)           | 13 (27.08%)      | 18 (27.27%)      | 0.70      |
| Hypertension                    | 66 (57.89%)           | 25 (52.08%)      | 41 (62.12%)      | 0.28      |
| COPD                            | 22 (19.29%)           | 11 (22.91%)      | 11 (16.66%)      | 0.40      |
| Atrial fibrillation             | 21 (18.42%)           | 1 (2.08%)        | 20 (30.30%)      | <0.01     |
| Coronary artery disease         | 22 (19.29%)           | 8 (16.66%)       | 14 (21.21%)      | 0.54      |
| History of malignancy           | 16 (14.03%)           | 7 (14.58%)       | 9 (13.63%)       | 0.88      |
| **Drugs on admission**          |                       |                  |                  |           |
| Beta-blocker                    | 35 (30.70%)           | 12 (25.00%)      | 23 (34.84%)      | 0.09      |
| ACE inhibitor                   | 35 (30.70%)           | 14 (29.16%)      | 21 (31.81%)      | 0.42      |
| ARB                             | 11 (9.64%)            | 4 (8.33%)        | 7 (10.60%)       | 0.75      |
| Aspirin                         | 29 (25.43%)           | 11 (22.91%)      | 18 (27.27%)      | 0.33      |
| Heparin                         | 2 (1.7%)              | 0 (0%)           | 2 (3.03%)        | 0.49      |
| Therapeutic anticoagulation     | 7 (6.14%)             | 2 (4.16%)        | 5 (7.57%)        | 0.45      |

Data are presented as mean ± SD or n (%), n = 114. *P values for the comparison between Takotsubo syndrome patients ≤ 65 years and > 65 years. ACE: angiotensin-converting-enzyme; ARB: angiotensin-receptor-blocker; BMI: body-mass-index; BP: blood pressure; CKMB: creatine kinase MB fraction; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction.
Table 2. Outcome of patients.

| In-hospital variables                                      | ≤ 65 yrs (n = 48)       | > 65 yrs (n = 66)       | P value |
|-----------------------------------------------------------|-------------------------|-------------------------|---------|
| Length of ICU stay                                         | 4.33 ± 4.82             | 4.50 ± 7.25             | 0.89    |
| Cardiogenic shock with Inotropic support                   | 11 (22.9%)              | 10 (15.1%)              | 0.29    |
| In-hospital death                                          | 11 (22.9%)              | 11 (11.6%)              | 0.61    |
| Resuscitation                                              | 5 (10.41%)              | 4 (6.06%)               | 0.48    |
| Mechanical respiratory support (invasive and non-invasive) | 20 (41.66%)             | 19 (28.78%)             | 0.15    |
| Malignant arrhythmias                                      | 7 (14.58%)              | 6 (9.09%)               | 0.36    |
| In-hospital death                                          | 3 (6.25%)               | 6 (9.09%)               | 0.73    |
| Thromboembolic events                                     | 5 (10.41%)              | 9 (13.63%)              | 0.77    |
| Acquired long QT syndrome                                  | 30 (62.50%)             | 43 (65.15%)             | 0.25    |
| Long-term events during follow-up                         |                         |                         |         |
| Death (all-cause)                                          | 13 (27.1%)              | 20 (30.3%)              | 0.70    |
| 30 days' mortality                                         | 3 (6.2%)                | 5 (7.5%)                | 1.00    |
| Unknown cause                                              | 1 (2.0%)                | 4 (6.0%)                | 0.39    |
| Cardiac cause                                              | 4 (8.3%)                | 7 (10.6%)               | 0.35    |
| Shock (HR: 2.6, 95% CI: 1.2–5.7; P = 0.01), C-reactive protein (HR: 1.0, 95% CI: 1.0-1.0; P < 0.01), glomerular filtration rate (GFR) < 60 mL/min (HR: 2.5, 95% CI: 1.2–5.1; P = 0.01), ejection fraction (EF) ≤ 35% (HR: 4.8, 95% CI: 2.2–104; P < 0.01), shock (HR: 4.1, 95% CI: 2.0–8.4; P < 0.01) and the use of inotropic drugs (HR: 3.9, 95% CI: 1.9–7.9; P < 0.01) were associated with the primary endpoint. In the multivariate Cox regression analysis, male gender (HR: 2.8, 95% CI: 1.1–7.2; P = 0.02), EF ≤ 35% (HR: 3.3, 95% CI: 1.2–9.2; P = 0.01) and GFR < 60 mL/min (HR: 3.1, 95% CI: 1.4–7.0; P < 0.01) were found to be independent predictors of mortality (Table 3). |
| Recurrence of TS                                           | 3 (6.2%)                | 4 (6.0%)                | 1.0     |
| Heart Failure                                              | 0 (0.0%)                | 6 (9.0%)                | 0.03    |
| Stroke                                                    | 0 (0.0%)                | 4 (6.0%)                | 0.13    |

Data are presented as mean ± SD or n (%). ICU: intensive care unit; TS: Takotsubo syndrome.

3.3 Long-term outcome

All patients included in this study were successfully followed-up. The long-term mortality was similar in both age groups (Table 2 and Figure 1); however, heart failure (6% vs. 0) and stroke (6% vs. 0) occurred more often in the older age group.

In the Cox univariate analysis, male gender (HR: 2.6, 95% CI: 1.2–5.7; P = 0.01), C-reactive protein (HR: 1.0, 95% CI: 1.0-1.0; P < 0.01), glomerular filtration rate (GFR) < 60 mL/min (HR: 2.5, 95% CI: 1.2–5.1; P = 0.01), ejection fraction (EF) ≤ 35% (HR: 4.8, 95% CI: 2.2–104; P < 0.01), shock (HR: 4.1, 95% CI: 2.0–8.4; P < 0.01) and the use of inotropic drugs (HR: 3.9, 95% CI: 1.9–7.9; P < 0.01) were associated with the primary endpoint. In the multivariate Cox regression analysis, male gender (HR: 2.8, 95% CI: 1.1–7.2; P = 0.02), EF ≤ 35% (HR: 3.3, 95% CI: 1.2–9.2; P = 0.01) and GFR < 60 mL/min (HR: 3.1, 95% CI: 1.4–7.0; P < 0.01) were found to be independent predictors of mortality (Table 3).

4 Discussion

Our study showed that (1) in-hospital mortality of TS is high; (2) the long-term mortality of TS patients increased during follow-up; (3) age does not impact the short- and long-term outcome of TS; and (4) the incidence of heart failure is higher in older patients.

TS is frequently quoted to be a benign disorder; however, the results of our study show high rates of complications, which could occur anytime in the course of the disease. In a similar TS register, complications were observed in almost 52% of the patients, with most responding successfully to clinical lines of management.[6]

Cardiogenic shock (18.4%), necessitating inotropic and

Figure 1. Kaplan-Meier survival curve in two age categories: ≤ 65 years and > 65 years.
Table 3. Multivariate analysis for the long-term mortality.

| Univariate analysis | Multivariate analysis |
|---------------------|-----------------------|
|                     | HR  | 95% CI   | P-value | HR  | 95% CI   | P value |
| Male                | 2.6 | 1.2–5.7  | 0.01    | 2.8 | 1.1–7.2  | 0.02    |
| CRP                 | 1.0 | 1.0–1.0  | < 0.01  | 1.0 | 0.9–1.0  | 0.36    |
| Age                 | 1.0 | 0.9–1.0  | 0.60    |      |          |         |
| GFR < 60 mL/min     | 2.5 | 1.2–5.1  | 0.01    | 3.1 | 1.4–7.0  | < 0.01  |
| Shock               | 4.1 | 2.0–8.4  | < 0.01  | 3.8 | 0.6–23.4 | 0.13    |
| EF ≤ 35%            | 4.8 | 2.2–104 | < 0.01  | 3.3 | 1.2–9.2  | 0.01    |
| Emotional stress    | 0.4 | 0.1–1.1  | 0.10    |      |          |         |
| Inotropic drugs     | 3.9 | 1.9–7.9  | < 0.01  | 0.4 | 0.0–2.8  | 0.40    |
| DM type II          | 1.0 | 0.7–1.4  | 0.81    |      |          |         |
| Hypertension        | 0.9 | 0.7–1.2  | 0.64    |      |          |         |
| Apical ballooning   | 1.1 | 0.8–1.4  | 0.39    |      |          |         |
| History of cancer   | 1.7 | 0.7–4.2  | 0.21    |      |          |         |
| Smoking             | 0.7 | 0.3–1.6  | 0.49    |      |          |         |

CRP: C-reactive protein; DM: diabetes mellitus; EF: ejection fraction; GFR: glomerular filtration rate; HR: hazard ratio.

respiratory support, was the most dramatic complication of the syndrome. Although the sympathetic activity hypothesis has been widely accepted as the likeliest cause of TS, there is currently no reliable data highlighting catecholamine concentrations during the acute phase. Data from the univariate analysis suggested that the use of inotropic drugs in our patient collective was associated with increased mortality (HR: 3.9; \( P < 0.01 \)), however, no such significance could be elicited in the multivariate analysis. As of now, the routine use of inotropic drugs in this situation is not recommended, as they probably exacerbate or prolong the acute phase.[16]

Life threatening arrhythmias were observed in 11.4% of our study patients, with a higher incidence rate documented in the younger age-group (14.5%). The other age-dependent difference was the higher incidence of stroke during follow-up among older adults (6% vs. 0). Stroke was intentionally included in our follow-up statistical evaluation, so as to include cases of thromboembolism, which is a known TS complication. There were no significant age-dependent differences in thromboembolic events between younger and older patients (10.4% vs. 13.6%; \( P = 0.77 \)). Thromboembolic events are common in TS and associated with higher mortality as compared to non-thromboembolic TS patients.[8,13]

Oral anticoagulation is recommended in cases of proven left ventricular thrombi, however, it is important to understand that, despite therapeutic anticoagulation, LV thrombi may grow and embolize.[6] It is possible that in the future, scoring systems or other pathways are developed to optimize the anticoagulation regime.

Another aspect of TS is the age-dependent occurrence of disease. A previous study reported that there is a significantly higher percentage of complications, readmission rates and chest pain recurrence in the elder patients’ cohort.[18]

In the Takotsubo Italian Network, age \( \geq 75 \) years as well as a lower LVEF on admission were independent predictors of in-hospital adverse events. Older adults (\( \geq 75 \) years) are known to generally have higher rates of in-hospital complications and in-hospital mortality (6.3% vs. 2.8% overall in-hospital mortality).[16,19]

The age of the patient was found to have a supplemental effect on in-hospital mortality following TS according to a predictive risk score. Patients with an age > 80 years had the highest odds ratio (OR) of mortality (OR from 3.06 up to 8.07 depending on age group), even after adjusting for multiple serious co-morbidities like shock, acute cerebrovascular disease or acute respiratory failure.[12] The score validation was based on the data of the US National Inpatient Sample (NIS). The other NIS based study revealed a poorer association between age and in-hospital mortality with marginal significance (OR: 1.03; 95% CI: 1.10–1.06; \( P = 0.04 \)).[13] This illustrates the fact that different results could be obtained even if a similar data source is used. Our results show that age was no significant factor for in-hospital mortality. We used both variables; continuous (per 1 year of age) and binary (above and below 65 years) for this study. Age was not considered a relevant factor predicting mortality, neither
between both groups (≤ 65 and > 65 years) nor in the univariate analysis (HR: 1.0; P = 0.60), for a duration of up to five follow-up years. As opposed to the NIS based studies, which deliver only in-hospital data, we analysed follow-up parameters for the duration of up to five years. Compared to age, the other clinical features such as male gender (HR: 3.8; P = 0.02), GFR < 60 mL/min (OR: 3.1; P < 0.01), shock (HR: 3.8; P = 0.12) and EF ≤ 35% (HR: 3.3; P < 0.01) were significantly better predictors of mortality. Male gender, kidney injury and shock were also risk factors in the in-hospital TS risk score.[12]

The other aspect of TS was the gender difference associated with the occurrence of disease. The fact that patients with TS are predominantly female has been well established.[20] In addition, various gender differences (mortality and life-threatening arrhythmia) in female and male subpopulations were reported in a number of studies.[6,21] It was shown that male gender was independently associated with composite cardiac events.[22] Further analysis of our study population revealed that male gender was associated with elevated mortality (HR: 2.6; 95% CI: 1.2–5.7; P < 0.01). In conclusion, we can assume that age is a risk factor for the occurrence of TC but has no influence on the clinical course and long-term mortality or prognosis.

One of the main limitations is the monocentric and retrospective design of the study. The results of the study should be interpreted with caution in the light of the small sample size. The events’ rate was relatively low and needs to be evaluated in large multicentre registries.

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