

Trigger factors in takotsubo syndrome – A systematic review of case reports

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ABSTRACT

Introduction: Takotsubo syndrome is an acute heart failure syndrome often preceded by a trigger factor of physical or emotional origin, although the proportion is unclear. The aim of the present study was to determine how common different trigger factors are in takotsubo syndrome divided by sex and age in women.

Material and methods: The study consisted of a systematic review of all available case reports in PubMed and Web of Science up to March 2018. Trigger factors were categorized into physical and emotional trigger factors. **Results:** Males had to a higher degree experienced a trigger factor (92.6%) compared to females (81.9%, $p < .001$). Physical trigger factors were most common (67.3%). Males had to a higher degree experienced a physical trigger factor (85.7%) compared to females (63.5%, $p < .001$). Females ≤ 50 years of age had to a higher degree experienced a trigger factor (90.8%) compared to females > 50 years of age (79.2%, $p < .001$). Additionally, females ≤ 50 years of age had to a higher degree experienced a physical trigger factor (75.6%) compared to females > 50 years of age (59.3%, $p < .01$).

Conclusion: A physical trigger factor is more common than an emotional trigger factor in takotsubo syndrome. Physical triggers includes drugs, surgery and central nervous system conditions. Furthermore, females ≤ 50 years of age and males more often have an evident trigger factor and it is more often physical, compared to the most common patient, a female > 50 years of age.

1. Introduction

Takotsubo syndrome is a relatively new condition first described in 1990 [1] and knowledge is still limited [2]. It could be considered an acute heart failure syndrome where the left ventricle contracts abnormally [3] without a corresponding coronary artery stenosis or plaque rupture [4]. The syndrome is associated with severe risks [2]. Takotsubo syndrome is more prevalent in certain groups. It is more common in females than in males (9:1 ratio) [2,5–7] and patients are predominantly post-menopausal females with a mean age of 70 [3] and several mechanisms associated with female menopause have been presented [2,6,8]. Trigger factors preceding the event of takotsubo syndrome are widely recognized [2,3,9,10]. The pathophysiology of takotsubo syndrome is however still unknown but an increased sympathetic activity with elevated levels of blood-borne catecholamines seems to contribute [5,11–13]. The trigger factor could be of either emotional or physical origin [2,14]. Recently, a classification of primary and secondary takotsubo syndrome has been suggested by Lyon et al. [10] that is based on if an emotional or physical trigger precede the event of takotsubo. In primary takotsubo syndrome, the reason for seeking medical help stems from the takotsubo-induced cardiac

symptoms [10]. A trigger factor, if present, is then often emotional [10]. Emotional triggers are considered causing a one-time traumatic event with a stressful reaction from the patient [3]. The patient often have comorbidities, nevertheless they are not the immediate reason for the sympathetic nervous system (SNS) activation [10]. In secondary takotsubo syndrome, the patient is, in contrary to primary takotsubo, already admitted to hospital for another medical, surgical, obstetric or psychiatric reason [10]. The activation of SNS then derives from a physical trigger factor associated with common acute illnesses or medical interventions [3,10]. Some of the described illnesses are chronic obstructive pulmonary disease (COPD), asthma [3,12], central nervous system diseases (subarachnoid haemorrhage, epilepsy, ischemic stroke) [15], endocrine disorders (thyrotoxicosis, syndrome of inappropriate secretion of antidiuretic hormone, Addisonian crisis) [10], anaemia [12], fracture, sepsis, malignancy [16], obstetric and gastrointestinal causes [10]. In addition, elective procedures could also initiate SNS activation [10], for example surgery [17], diagnostic stress echocardiography, electroconvulsive therapy and drug administration [12]. In 30% of the cases there is no known trigger factor [2,18]. There are also indications of variation between different demographic groups regarding proportions of emotional and physical trigger factors in

Abbreviations: β AR, Beta adrenergic receptor; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; SNS, sympathetic nervous system

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Table 1
Search strategy for takotsubo case reports.

Database: Web of Science Date: 02-04-2018 #1	Search words (MeSH-terms and free text) ((takotsubo* OR tako-tsubo OR TCM OR "apical ballooning*" OR "tako tsubo")) AND (case*)	Limitations (Filter, Limits, Refine)	Hits
Database: PubMed Date: 02-04-2018 #1	Takotsubo [MeSH]	Case reports	2017
			1544

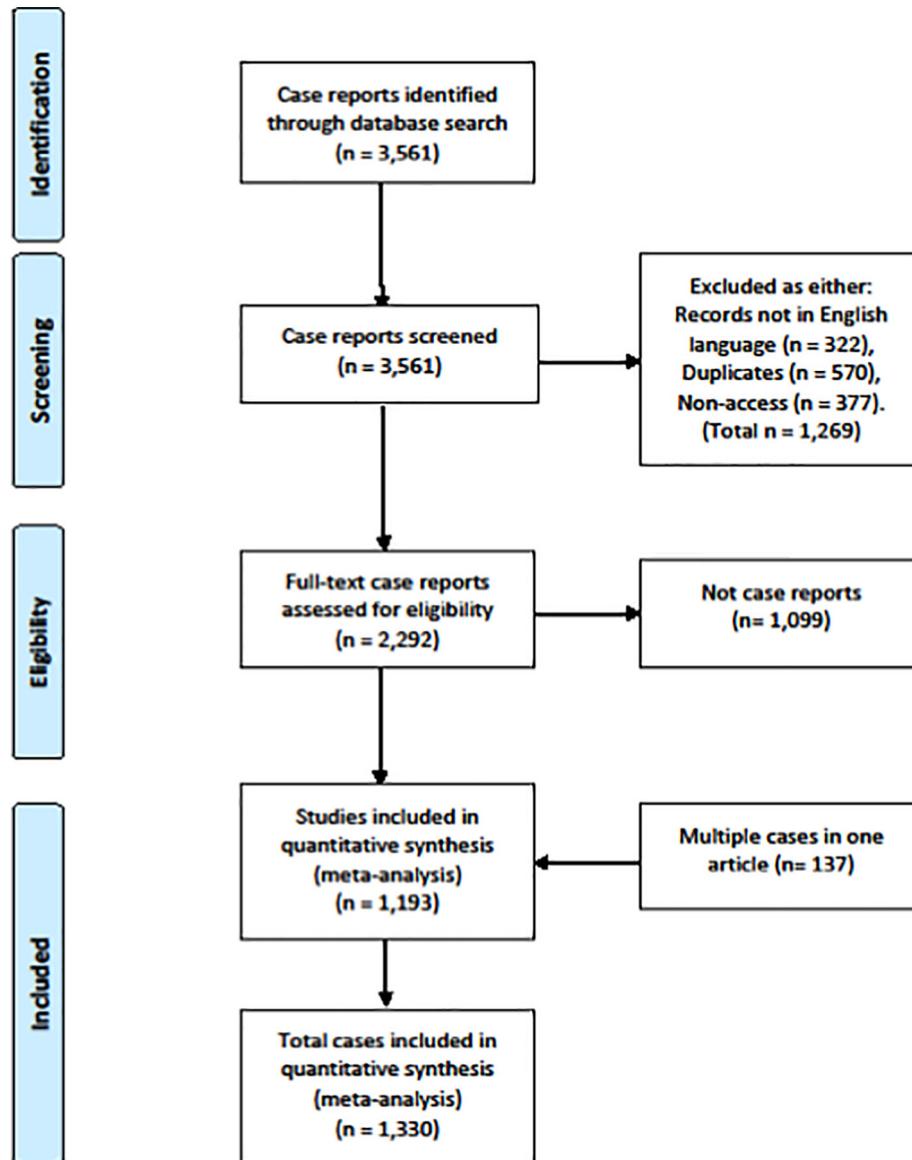


Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of meta-analysis of takotsubo patient case reports. Number of included takotsubo patient case reports and reasons for exclusion. Non-access implicates lack of access by the Karolinska Institutet Library.

takotsubo syndrome. Females tend to more often have an emotional trigger [2,19]. Patel et al. [19] suggested that young females (< 50 years of age) more often had a physical than emotional trigger factor compared to elderly females (≥ 50 years of age). Since studies concerning trigger factors in takotsubo syndrome are limited in size and reliability, further research is desirable. Moreover, there are few systematic reviews on the topic but a large number of case reports accessible in scientific literature. To our knowledge, takotsubo case reports have not been analyzed in total. Thus the aim of this study was therefore to identify trigger factors for takotsubo syndrome and compare the trigger factors between females and males and also between

females ≤ 50 years of age and females > 50 years of age by performing a systematic review of case reports.

2. Materials and methods

2.1. Study design

This study was a systematic review of case reports. The material consisted of patients from takotsubo case reports collected from PubMed and Web of Science using search strategies shown in Table 1. The inclusion criterion was a case-report with patient (s) diagnosed

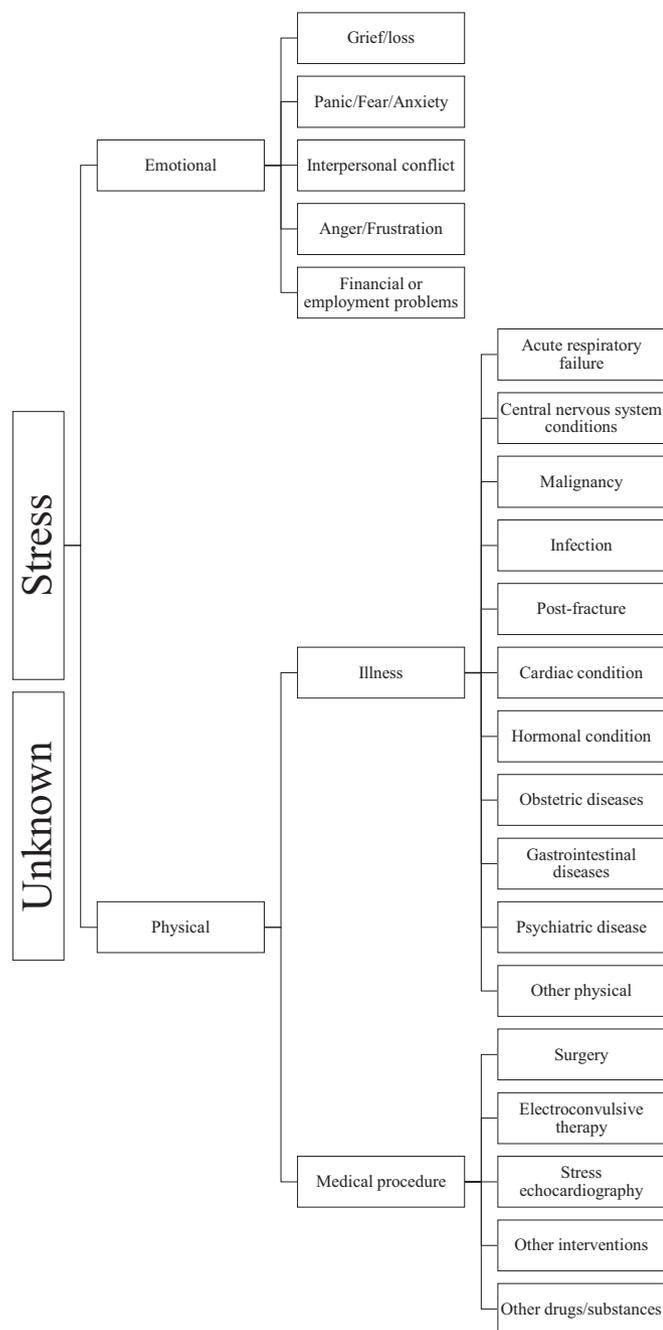


Fig. 2. Trigger factor categories.

with takotsubo syndrome by the medical care-givers. The original material was then further investigated, excluding non-English publications, duplicates and publications where the investigator did not have access using the Karolinska Institutet Library [20], see Fig. 1. All ages, sexes and publication dates were accepted. Material collected spanned from July 2000 to Mars 2018. A total of 1330 case reports were included in final analysis (Attachment 1). Age was collected as discrete data. Information about trigger factor, sex, if patient smoked, previously smoked, family history of takotsubo, family history of coronary artery disease (CAD) and comorbidity with hypertension, hyperlipidemia, diabetes mellitus, asthma, COPD, rheumatoid arthritis, hypothyroidism and psychiatric disorder were collected as categorical data. The population was then divided into subgroups, female/male and females ≤ 50 years of age/females > 50 years of age.

Table 2
Patient characteristics of all available takotsubo patients from case reports year 2000 to March 2018.

Patient characteristics	Takotsubo patients (n = 1330)	
	Number	(%)
Age	60	(SD 18.3)
Female	1121	(84.6%)
Female ≤ 50 years of age	262	(19.7%)
Female > 50 years of age	859	(64.6%)
Male	204	(15.4%)
Smoker	81	(6.1%)
Earlier smoker	118	(8.9%)
Heritability takotsubo syndrome	1	(0.1%)
Heritability coronary artery disease	42	(3.2%)
Co-morbidities		
Hypertension	377	(28.3%)
Hyperlipedemia	153	(11.5%)
Diabetes Mellitus	87	(6.5%)
Asthma	42	(3.2%)
Chronic obstructive pulmonary disease	47	(3.5%)
Rheumatism	19	(1.4%)
Hypothyroidism	48	(3.6%)
Psychiatric disorder	124	(9.3%)

Abbreviations: n = number of participants, SD = standard deviation.

Table 3
Patient trigger factors of all available takotsubo patients in case reports year 2000 to March 2018.

Trigger factors	Takotsubo patients (n = 1330)	
	Number	(%)*
No stress/Unknown	218	(16.4%)
Stress	1112	(83.6%)
Emotional	364	(32.7%)
Grief/Loss	84	(23.1%)
Panic/Fear/Anxiety	115	(31.6%)
Interpersonal conflict	18	(4.9%)
Anger/Frustration	60	(16.5%)
Financial/Employment problems	19	(5.2%)
Other/Unspecified	68	(18.7%)
Physical	748	(67.3%)
Illness	449	(60.0%)
Acute respiratory failure	36	(8.0%)
Central nervous system conditions	100	(22.3%)
Malignancy	7	(1.6%)
Infection	55	(12.2%)
Post-fracture	8	(1.8%)
Cardiac condition	25	(5.6%)
Hormonal condition	64	(14.3%)
Obstetric condition	26	(5.8%)
Gastrointestinal disease	24	(5.3%)
Psychiatric disease	14	(3.1%)
Other physical	90	(20.0%)
Medical procedures	299	(40.0%)
Surgery	115	(38.5%)
Electroconvulsive therapy	9	(3.0%)
Stress echocardiography	17	(5.7%)
Other interventions	41	(13.7%)
Other drugs/substances	117	(39.1%)

Abbreviations: n = number of participants.

* Percentage calculated within each trigger factor subgroup.

2.2. Definitions of categories and other data

Trigger factors were manually categorized into different subgroups. Stress was chosen if there was an immediate preceding trigger factor within 12 h of the takotsubo event [3]. In the event of no mentioned trigger factor the patient was included into the category “No stress/Unknown”. The trigger factors were first divided into “emotional” and “physical” stress. Emotional triggers included stressful events in

Table 4
Trigger factors of takotsubo patients from case reports with sex comparison.

	Female number (%) ^a	Male number (%) ^a	p-Value ^{**}
Age	61 (SD 17.5)	52 (SD 20.8)	
Trigger factors			
No stress/Unknown	203 (18.1%)	15 (7.4%)	< .001
Stress	918 (81.9%)	189 (92.6%)	< .001
Emotional	335 (36.5%)	27 (14.3%)	< .001
Grief/Loss	78 (23.3%)	6 (22.2%)	n.s.
Panic/Fear/Anxiety	104 (31.0%)	10 (37.0%)	n.s.
Interpersonal conflict	18 (5.4%)	–	n.s.
Anger/Frustration	55 (16.4%)	5 (18.5%)	n.s.
Financial/Employment problems	17 (5.1%)	2 (7.4%)	n.s.
Other/Unspecified	63 (18.8%)	4 (14.8%)	n.s.
Physical	583 (63.5%)	162 (85.7%)	< .001
Illness	352 (60.4%)	94 (58.0%)	n.s.
Acute respiratory failure	31 (8.8%)	5 (5.3%)	n.s.
Central nervous system conditions	76 (21.6%)	22 (23.4%)	n.s.
Malignancy	6 (1.7%)	1 (1.1%)	n.s.
Infection	39 (11.1%)	16 (17.0%)	n.s.
Post-fracture	6 (1.7%)	2 (2.1%)	n.s.
Cardiac condition	22 (6.3%)	3 (3.2%)	n.s.
Hormonal condition	45 (12.8%)	18 (19.1%)	n.s.
Obstetric condition	26 (7.4%)	–	n.s.
Gastrointestinal disease	21 (6.0%)	3 (3.2%)	n.s.
Psychiatric disease	13 (3.7%)	1 (1.1%)	n.s.
Other physical	67 (19.0%)	23 (24.5%)	n.s.
Medical procedures	231 (39.6%)	68 (42.0%)	n.s.
Surgery	90 (39.0%)	25 (36.8%)	n.s.
Electroconvulsive therapy	7 (3.0%)	2 (2.9%)	n.s.
Stress echocardiography	15 (6.5%)	2 (2.9%)	n.s.
Other interventions	31 (13.4%)	10 (14.7%)	n.s.
Other drugs/substances	88 (38.1%)	29 (42.6%)	n.s.

Abbreviations: SD = standard deviation, n.s. = non-significant.

^a Percentage calculated within each trigger factor subgroup.

^{**} p-Values for comparison of patient trigger factors between females and males were calculated with Chi2-test.

personal and working life, and physical triggers included acute illnesses, medical procedures and diagnostic tests [3].

Emotional trigger factors were further divided; “Grief/Loss” was chosen if the patient was notified of someone's death or near death or had a remembrance of someone's death, for example tenth anniversary of son's death. “Panic/Fear/Anxiety” was chosen if there was a traumatic event leading to feelings of and/or an anxiety attack, for example falling outdoors and fearing freezing to death. “Interpersonal conflict” was chosen if there was a stressful relationship, sometimes a cumulative event, for example lengthy divorce with the sale of patient's home of the last 28 years. “Anger/Frustration” was chosen if there was a sudden outburst of anger and frustration, for example a heated argument with a family member. “Financial/Employment problems” was chosen if the stress included money issues or event at work, for example stressful beginning to a new occupation. The emotional trigger factors that did not fall into either of these categories were placed in “Others”. The descriptions are according to Sharkey et al. [3] and Templin et al. [2].

The physical trigger factors were further divided into two groups; “Illness” a condition that the patient had had before the event of takotsubo or “Medical procedure” that was defined as takotsubo syndrome in association with treatments and diagnostic tests. “Illness” was further divided; “Acute respiratory failure” was considered acute onset of respiratory difficulties with origin from the respiratory tract, for example exacerbation of COPD, status asthmaticus, pulmonary embolism and obstruction of respiratory passage. “Central nervous system conditions” included acute conditions originating from the central nervous system, for example subarachnoid haemorrhage, brain contusion, ruptured cerebral aneurysm, seizure and vasculitis. “Malignancy” was considered if takotsubo event was directly due to symptoms from

the malignancy. “Infection” included all acute infections, for example urosepsis and peritonitis. The descriptions are according to Sharkey et al. [3] and Templin et al. [2]. However, additions were made to further describe different physical trigger factors. These additional categories were chosen with help of the current literature [3] and experience gathered during the analysis of the case reports. The category “Other” by Sharkey et al. [3] in the “Physical” group was divided further into the following events; “Cardiac condition” for example acute heart failure, “Hormonal condition” for example diseases of the thyroid, “Obstetric diseases” for example miscarriage and labour, “Gastrointestinal diseases” for example acute cholecystitis and severe diarrhea, excluding known infections, “Psychiatric disease” for example delirium, “Other physical”, “Electroconvulsive therapy”, “Stress echocardiography”, “Other interventions” and “Other drugs/substances”. The group “Post-surgical/fracture” was further divided into “Surgery” and “Post-fracture” (orthopedic fractures). If more than one trigger factor was mentioned, only the most recent trigger factor before the event of takotsubo was chosen. These trigger factor subgroups are illustrated in Fig. 2.

Additionally, from the case reports data about medical history were collected. The conditions were only considered when recorded by the authors of the case reports. To be considered a negative answer the author should have freed the patients from it in writing or included other data telling against it, for example low values of blood pressure. If nothing was mentioned about the specific data, it was considered unknown.

2.3. Statistics

Categorical variables were described in frequencies and percentages, age with mean and SD. Chi2-test was used to compare females with males and also females ≤ 50 years of age with females > 50 years of age regarding difference in trigger factors, due to the categorical nature of the data collected. All comparisons were made in the statistical program SPSS (IBM) version 23. A two-tailed significance level of < 0.05 was considered significant.

3. Results

The mean age was 60 years among all takotsubo patients. Females represented 85% of the patients, females over the age of 50 represented two thirds of the patients. The characteristics of the patients from the takotsubo case reports (n = 1330) are described in Table 2. A trigger factor was present in 83.6% of the cases. Physical were more frequent than emotional trigger factors. Takotsubo syndrome in response to illness was more frequent than to medical procedures. “Central nervous system conditions” and “other physical” were most frequent of the illnesses. “Other drugs/substances” and “surgery” were most frequent of the medical procedures. The most common emotional trigger factors were “Panic/Fear/Anxiety” and “Grief/Loss”. More detailed information is available in Table 3. “Other physical” included for example electrolyte imbalances, musculoskeletal disorders, hematologic disorders and trauma. A broad variety of different drugs, recorded in “Other drugs/substances” were mentioned in the case reports. Although, the most common drugs mentioned were chemotherapy, adrenalin and street drugs.

Male takotsubo patients had a higher frequency of experienced trigger factor compared to the female takotsubo patients. Also, males experienced a physical trigger factor to a higher degree than females. Takotsubo trigger factors divided into females and males are shown in Table 4.

The population of females ≤ 50 years of age had a higher frequency of experienced trigger factor compared to the population of females > 50 years of age. Also, the younger females experienced a physical trigger factor to a higher degree than the population of older females. Trigger factors divided into females ≤ 50 years of age and >

Table 5Trigger factors in female takotsubo patients from case reports with subgrouping of females \leq and $>$ 50 years of age.

	Females \leq 50 years of age number (%) [*]	Females $>$ 50 years of age number (%) [*]	p-Value ^{**}
Age	35 (SD 11.4)	69 (SD 9.8)	
Trigger factors			
No stress/Unknown	24 (9.2%)	179 (20.8%)	< .001
Stress	238 (90.8%)	680 (79.2%)	< .001
Emotional	58 (24.4%)	277 (40.7%)	< .01
Grief/Loss	12 (20.7%)	66 (23.8%)	n.s.
Panic/Fear/Anxiety	16 (27.6%)	88 (31.8%)	n.s.
Interpersonal conflict	6 (10.3%)	12 (4.3%)	n.s.
Anger/Frustration	12 (20.7%)	43 (15.5%)	n.s.
Financial/Employment problems	4 (6.9%)	13 (4.7%)	n.s.
Other/Unspecified	8 (13.8%)	55 (19.9%)	n.s.
Physical	180 (75.6%)	403 (59.3%)	< .01
Illness	104 (57.8%)	248 (61.5%)	n.s.
Acute respiratory failure	3 (2.9%)	28 (11.3%)	n.s.
Central nervous system conditions	26 (25.0%)	50 (20.2%)	n.s.
Malignancy	1 (1.0%)	5 (2.0%)	n.s.
Infection	5 (4.8%)	34 (13.7%)	n.s.
Post-fracture	1 (1.0%)	5 (2.0%)	n.s.
Cardiac condition	1 (1.0%)	21 (8.5%)	n.s.
Hormonal condition	15 (14.4%)	30 (12.1%)	n.s.
Obstetric condition	26 (25.0%)	–	< .001
Gastrointestinal disease	4 (3.8%)	17 (6.9%)	n.s.
Psychiatric disease	5 (4.8%)	8 (3.2%)	n.s.
Other physical	17 (16.3%)	50 (20.2%)	n.s.
Medical procedures	76 (42.2%)	155 (38.5%)	n.s.
Surgery	37 (48.7%)	53 (34.2%)	n.s.
Electroconvulsive therapy	1 (1.3%)	6 (3.9%)	n.s.
Stress echocardiography	1 (1.3%)	14 (9.0%)	n.s.
Other interventions	4 (5.2%)	27 (17.4%)	n.s.
Other drugs/substances	33 (43.4%)	55 (35.5%)	n.s.

Abbreviations: SD = standard deviation, n.s. = non-significant.

^{*} Percentage calculated within each trigger factor subgroup.^{**} p-Values for comparison of patient trigger factors between females \leq and $>$ 50 years of age were calculated with Chi2-test.**Fig. 3.** Takotsubo age distribution related to sex.

50 years of age are shown in Table 5.

The mean age for female patients was 61 and the mean age for male patients was 52 (Table 4). Males tended to have a more even distribution of takotsubo prevalence throughout life compared to females, illustrated in Fig. 3. The prevalence was similar until the age of 30 when there was a tendency of the female prevalence to rise. After the age of 50 the female prevalence tended to increase rapidly until the age of 70. After 75 years of age the female prevalence rapidly declined.

4. Discussion

This study, based on a systematic review of case reports, presented data on trigger factors preceding takotsubo syndrome. The results showed that physical trigger factors were more common than emotional trigger factors. The results also showed that females \leq 50 years of age and males to a high degree experienced a trigger factor before the event of takotsubo syndrome with a predominance for physical trigger factors.

This study showed that takotsubo patients experienced a trigger

factor in 8 of 10 cases. The results are concordant with the results of Templin et al. [2] and Sharkey et al. [3], where 7 of 10 patients and 9 of 10 patients experienced a trigger factor, respectively. Physical trigger factors seems to be more common than emotional trigger factors [2], although Sharkey et al. [3] showed the opposite relationship. Initially only trigger factors of emotional origin were discussed [11,21]. The recognition of physical trigger factors in takotsubo syndrome was only recently accepted [9,14]. This study further emphasizes the substantial portion of takotsubo syndrome events which are preceded by physical trigger factors. The distribution of the emotional and physical triggers in this study corresponds well with the results by Templin et al. [2]. Panic/Fear/Anxiety was the most prevalent category of the emotional triggers, known to give a strong reaction from the SNS. Central nervous system conditions were the most frequent of the illnesses, suggesting a neurological pathophysiology since neurons from the brain stem innervate the heart [13], however the mechanisms are not clear. Furthermore, surgery was one of the most frequent trigger factors of the medical procedures. Surgery is a multifactorial procedure and the exact triggering factor is complicated to distinguish. However, according to a review by Agarwal et al. [17] general anesthesia and the first post-operative period seemed to be the most perilous. One of the other common trigger factor categories for takotsubo syndrome was drugs and substances, indicating the importance of cautiousness and awareness of the syndrome when administering drugs, especially chemotherapy and adrenalin. These risk drugs have earlier been identified [22,23]. Of note, malignancy only contributed to a negligible amount of takotsubo cases, contradicting a paraneoplastic phenomenon suggested by Burgdorf et al. [24]. Instead the high prevalence of takotsubo syndrome among patients with malignancy [2] could be contributed by the high frequency of surgery, chemotherapy and emotional stress among this patient group.

Females represented 85% of the patients and the mean age was 61 years. The sex distribution and mean age in this study corresponded well with the results by others [2,3,25] and could therefore be suggested to be representative of the takotsubo population. The female takotsubo population > 50 years of age was considerable larger than the female takotsubo population ≤ 50 years of age. The females ≤ 50 years of age had to a higher degree experienced a trigger factor before takotsubo and the trigger factor was more often physical, compared to females > 50 years of age, corroborating the result by Patel et al. [19], the only study discerning the subject so far. When comparing females and males, males tended to have a higher degree of experienced trigger factors before takotsubo, also seen in the study by Patel et al. [19]. On the contrary, Templin et al. [2] noted no difference between females and males. Males seemed to have a physical trigger factor more often than females, corroborating the result by Templin et al. [2], Patel et al. [19] and Schneider et al. [25]. Along with females ≤ 50 years of age, males seem to have another panorama of trigger factors and a lower prevalence of takotsubo syndrome, suggesting a pathophysiological difference, possibly introduced by menopause in women, as suggested by others [6,26]. In support of this is that sex hormones influence SNS [27] but also coronary vasoreactivity [28]. Furthermore, in a rat model, after ovariectomy, infusion of estradiol reduced stress-induced dysfunction [8], implying the role of female menopause in takotsubo syndrome. One of the possible explanations included the loss of estrogen-mediated suppression of βAR expression in the myocardium and vasculature [8]. However, the role of menopause could be challenged since in the case reports the female prevalence of takotsubo syndrome increased as early as after 30 years of age.

The clinical relevance of the present findings is that we show that the most common takotsubo patient is a woman > 50 years of age with an emotional trigger factor. This supports the use of the InterTAK diagnostic score [29] since female sex with an emotional trigger has a sensitivity of 89% and specificity of 91% to diagnose takotsubo. Furthermore, the findings that physical trigger factors are common in women ≤ 50 years of age and men should increase the awareness that

takotsubo is an important differential diagnosis to myocardial infarction in these patients when having cardiac symptoms during illnesses and medical procedures.

The limitations of this study are that there was no further contact with the authors of the case reports to fill in missing information, the descriptions of the emotional trigger factors were sometimes subjective, the retrospective nature and publication bias. The publication bias could interfere with generalization to the typical takotsubo patient since more challenging cases are more likely to be published. However, the proportion of no evident trigger factor was similar to other studies, which could indicate a comparable representativity.

5. Conclusions

A physical trigger factor is more common than an emotional trigger factor in takotsubo syndrome. Physical triggers included drugs, surgery and central nervous system conditions. Furthermore, females ≤ 50 years of age and males more often have an evident trigger factor and it is more often physical, compared to the most common patient, a female > 50 years of age.

Conflict of interest

None of the authors have any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejim.2019.02.017>.

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