Current Problems in Cardiology 49 (2024) 102804

Contents lists available at ScienceDirect

Current Problems in Cardiology

journal homepage: www.elsevier.com/locate/cpcardiol

Invited Review Article

Chronobiological variation in takotsubo syndrome: an updated systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Takotsubo syndrome
Stress cardiomyopathy
Chronobiology
Circadian rhythm
Seasons
Day-of-week
Sex differences

ABSTRACT

Takotsubo syndrome (TTS) might exhibit particular chronobiological patterns in its onset, characterized by variations according to time of the day, day of the week, and month of the year.

The aim of this study was to fully explore the temporal patterns (circadian, weekly and seasonal) in the onset of TTS. A systematic review and meta-analysis of literature were conducted for studies (2006-2024) reporting the temporal patterns (circadian, weekly and/or seasonal) in the onset of TTS. Among the 4257 studies retrieved, 20 (including 64,567 subjects) fulfilled all eligibility criteria. Data were aggregated used random effects model as pooled risk ratio and the attributable risk (AR).

The proportion analysis (including 8 studies; n=853) showed a decreasing pattern of the pooled rates of TTS shifting from the morning to the night (pooled TTS rates: 34.0%; 32.1%; 21.7%; 12.7% in the morning, afternoon, evening and night, respectively). The same pattern was observed stratifying by type of preceding stressful factor or event, considering physical stressors (pooled rates in the morning and night: 37.6% and 9.8%, respectively), and also in case no event could be identified.

The pooled rates of TTS onset peaked on Monday and Tuesday (17.3% and 18.4% respectively), then declined during the week, reaching the lowest rates on Friday and Saturday (10.6% and 10.8%, respectively), with no sex differences. TTS onset reached the highest values on summer, and the lowest in winter (27.9% versus 21.7% in summer and winter, respectively). The TTS

Abbreviations: TTS, Takotsubo syndrome; RR, relative risk; AR, attributable risk; PAR, population attributable risk; CI, confidence interval.

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https://doi.org/10.1016/j.cpcardiol.2024.102804

Available online 18 August 2024

morning peak based analyses (∼33% of all the registered events) account for a RR of 1.46 (95% CI: 1.38-1.54), the week-based for a RR of 1.26 (1.16-1.35), the season-based for a RR of 1.04 (1.04-1.05).

TTS onset exhibits specific chronobiological patterns, characterized by a peak during the morning hours, and on Monday and Tuesday. Differing from other cardiovascular emergencies TTS was more frequent during summer. Further studies are needed to fully understand the underlying pathophysiological mechanisms in order to tailor relative management and preventive strategies.

Introduction

Takotsubo syndrome (TTS) is an acute heart failure syndrome characterized by transient left ventricular systolic dysfunction in the absence of significant coronary artery disease, occurring mostly in postmenopausal women after emotional and/or physical stress.[1-3] Patients with TTS commonly present with symptoms and signs indistinguishable from acute coronary syndrome (ACS)[2,3] (Fig. 1).

In recent years the reported TTS incidence was significantly increased,[1] approximately 2% of patients with suspected ACS have TTS. Furthermore, TTS in-hospital mortality (4-5%) is comparable to ACS.[2,3]

Interestingly, TTS might exhibit, as other cardiovascular emergencies, particular chronobiological patterns in its onset, characterized by variations according to time of the day, day of the week, and month of the year.[1]

Thus, the aim of the present systematic review and meta-analysis was to fully explore the temporal patterns (circadian, weekly and/or seasonal) in the onset of TTS.

Materials and methods

A systematic review and meta-analysis of literature were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA)[4] using a prespecified protocol (PROSPERO registry ID: CRD42024570235).

Study selection and eligibility criteria

MedLine and Scopus databases were searched to identify studies evaluating the temporal patterns (circadian, weekly and/or seasonal) in the onset of TTS. The bibliographic search was performed by 2 independent investigators (AC, MF) up to 31 December 2023, using the following search terms: Takotsubo cardiomyopathy OR Takotsubo syndrome OR transient left ventricular apical ballooning syndrome OR Takotsubo-like left ventricular dysfunction OR ampulla cardiomyopathy OR apical ballooning AND chronobiology OR circadian variation OR seasonal variation OR weekly variation.[5] While maintaining a common overall architecture, several alternative strings were used, after adjustment for each database. The reference lists of reviews and retrieved articles were also searched for additional pertinent papers, and no language or date restrictions were used. Inclusion criteria were: (a) cohort or case-control design; (b) inclusion of patients (≥18 years) with TTS as primary diagnosis, formulated in accordance with the accepted diagnostic criteria[6]; (c) provision of detailed data on the (1) circadian, (2) weekly, (3) seasonal pattern of occurrence of TTS.

For the analysis on the circadian pattern, the time of symptoms onset was categorized into four six-hour intervals (morning: 6:00 to 11:59 am; afternoon: 12:00 to 5:59 pm; evening: 6:00 to 11:59 pm; night: 12:00 to 5:59 am). For weekly analysis, the week was divided into seven one-day blocks. Three-month periods were used to classify the seasonal pattern of onset (spring: March to May; summer: June to August; autumn: September to November; winter: December to February). When the same population was reported more than once,[7-9] only the most descriptive report for each pattern of analysis was included. In one study,[10] the circadian onset of TTS was reported across periods of 12 hours: in this case, we computed from the other studies the summary mean percentage of events for each period, and applied the resulting proportions to the available data.

Quality assessment

Individual study quality was assessed using an adapted version of the Newcastle Ottawa Quality Assessment Scale, evaluating the comparability across groups at baseline for confounding factors (and examining whether analyses were adjusted adequately for confounders), the appropriateness of outcome assessment, length of follow-up and missing data handling and reporting.[11]

Statistical analysis

Meta-analyses of proportions was performed, combining the rates of TTS occurrence (a) in each period of the day; (b) in each day of the week; (c) in each season of the year to estimate circadian, weekly and seasonal pooled TTS rates, respectively. In order to account for between-study heterogeneity, a random-effect approach was used. Moreover, for each chronobiological pattern, five stratified meta-analyses were carried out to assess the pooled TTS rates (a) among males; (b) among females; (c) according to the existence of preceding stressful factors or events (physical, psychological or idiopathic – no stressor factor identified) which may have played a role in the aetiology of TTS.[12] Thus, a total of 15 separate meta-analyses were performed.

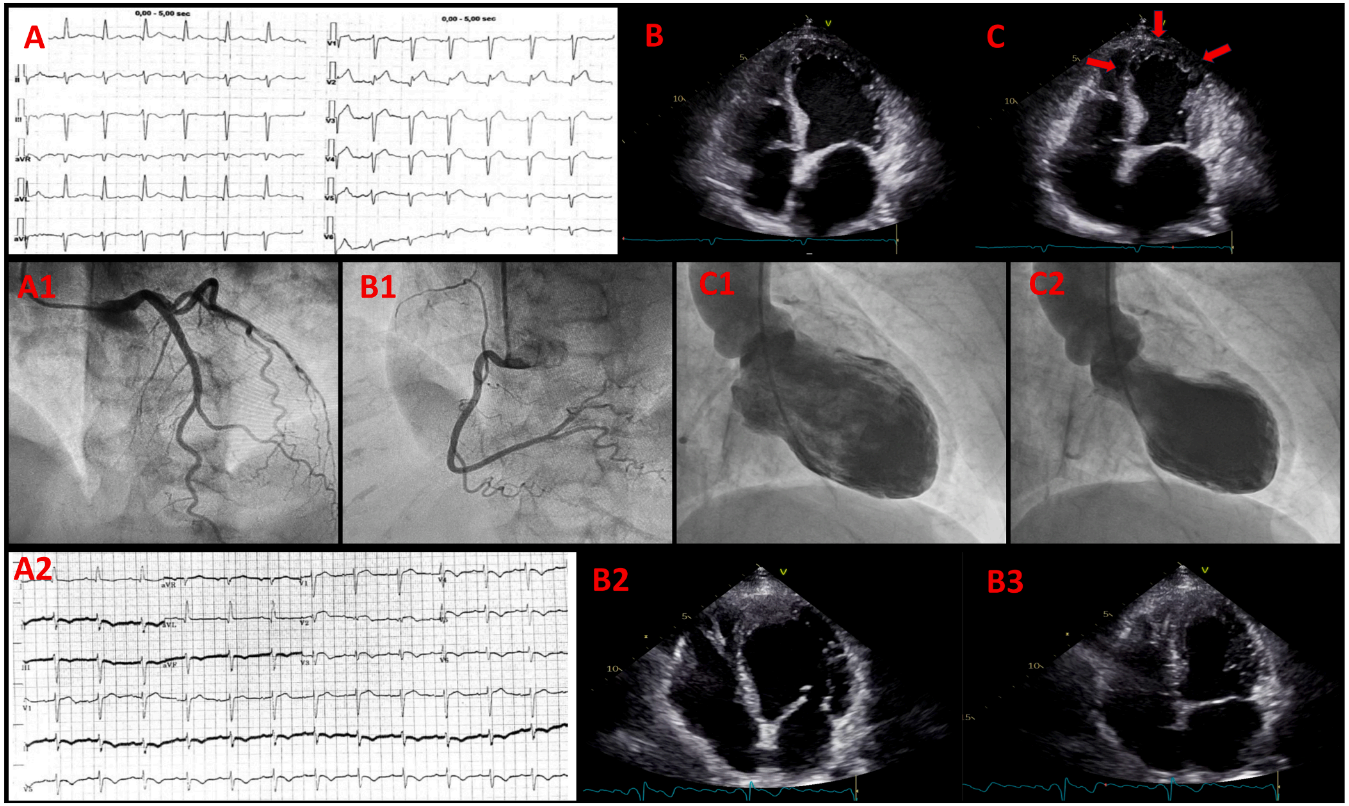

Fig. 1. A case of 58-year-old female with Takotsubo syndrome (TTS). At a presentation, ECG showed ST-segment elevations in the anterior precordial leads (A). Echocardiography revealed a left ventricle with normal contraction of the basal segments but akinesia and ballooning of the apical segments with reduced left ventricular ejection fraction (LVEF) of 40% (B and C). The coronary angiography was normal, with no significant occlusions or stenosis (A1, B1) and the left ventriculogram shows characteristic regional wall-motion abnormalities involving the apical segments (C1, C2). The patient revealed a recent emotional stress related to her sister's death. After 4 weeks from the discharge, ECG showed only an inverted T wave in anterior precordial leads (A2) and at echocardiography, LVEF was improved to 55% with no wall motion abnormality of the left ventricle (B2, B3).

Table 1
Characteristics of the included studies.

First author	Year	Country	Study years	Population - Setting	Total sample (% females)	Mean age	Pattern of analysis
Abdulla[17]	2006	Australia	1999-2004	AMI patients undergoing angiography extracted from the hospital database; TTS patients identied with differential diagnosis criteria (presence of segmental wall motion anomalies; no revascularization; no pericarditis or miocarditis; no troponin rise)	35 (97)	68	C*; S
Hertting[18]	2006	Germany	2001-2004	Retrospective analysis of all patients undergoing angiography; TTS patients identified with: (a) no atherosclerotic coronary narrowing; (b) LV motion anomalies	32 (91)	67.5	S
Kurisu[19]	2007	Japan	NR	Retrospective analysis of all patients admitted to the Cardiology Unit of the Hiroshima hospital; TTS patients identified with: (a) no atherosclerotic coronary narrowing; (b) LV motion anomalies	37 (89.2)	72	C
Citro[7]	2009	Italy	2002-2007	Retrospective analysis of all TTS patients admitted to the Coronary Units of 7 cardiac referral centers (Mayo criteria)	88 (94.4)	64.4	C; S
Regnante[20]	2009	US	2004-2008	Retrospective analysis of all TTS patients admitted to the Cardiology Units of 2 Rhode Island hospitals (Mayo criteria)	59 (95)	67	S
Manfredini[9]	2010	Italy	2002-2008	Retrospective analysis of all TTS patients admitted to the Coronary Units of 8 cardiac centers of the Takotsubo Italian Network (Mayo criteria)	112 (92.9)	63.6	W
Mansecal[21]	2010	France	2000-2008	Retrospective analysis of all TTS patients admitted to the Cardiology Unit (Mayo criteria)	51 (98)	71	C; S
Summers[22]	2010	US	2004-2008	Retrospective analysis of all TTS patients admitted to the Mayo Clinic	186 (NR)	NR	S
Parodi[23]	2011	Italy	2003-2008	Prospective analysis of all TTS patients admitted to the Cardiology Units of 5 Italian hospitals (Mayo criteria)	116 (NR)	NR	S
Sharkey[24]	2012	US	2001-2010	Retrospective analysis of all patients presented with TTS at the emergency and hospital facilities of 2 Minneapolis hospitals	186 (95)	68	C; W; S
Nascimento[10]	2013	US	2005-2009	Retrospective analysis of all patients undergoing echocardiography; TTS patients identified according to the Mayo diagnostic criteria	50 (62)	73.9	C; S
Song[12]	2013	Korea	2004-2010	Retrospective analysis of all patients included in the TTS Registry and admitted to 2 University Hospitals (Mayo diagnostic criteria)	137 (174)	59	C; W; S
Aryal[25]	2014	US	2009-2011	Data extracted from the AHRQ Nationwide Inpatient Sample database, using ICD9-CM codes for TTS	10,989 (NR)	NR	S
Novo[26]	2016	Italy	2011-2014	Retrospective analysis of all TTS patients admitted to the Cardiology Units of 3 Italian hospitals (Mayo criteria)	85 (93)	65	S
Isogai[27]	2017	Japan	2011-2013	Data extracted from the Japanese DPC database, including data from 1000 hospitals; TTS patients identified through: (a) ICD10 codes I42.8, I42.9, 151.8; (b) age >=20y; (c) no post-angiography revascularization	4306 (78.6)	73.6	S
Looi[28]	2018	New Zealand	2004-2016	Prospective analysis of all patients admitted to the Coronary Units of 2 Auckland Hospitals (Mayo criteria)	260 (95)	66	S
Kanaoka[29]	2020	Japan	2012-2016	Data extracted from the Japanese DPC database (Osaka, Kumamoto, Nara prefectures); TTC patients identified through: (a) ICD10 code 151.8; (b) age >=20y; (c)need of coronary angiography	5643 (79)	74	S
El-Battrawy[30]	2021	Germany	2003-2015	Retrospective analysis of all TTC patients admitted to the Mannheim Medical Faculty (Mayo criteria)	114 (83)	67	C; W; S
Yoshizawa[31]	2021	Japan	1997-2014	Retrospective analysis of all TTC patients admitted to the Cardiology Units of 10 teaching hospitals (Circ8-U Consortium) (Mayo criteria)	251 (78.5)	71.6	C; S*
Desai[32]	2023	US	2019	Data extracted from the National Inpatient Sample database, using ICD-10 code I51.81	41,830 (82.1)	69	S

TTS = Takotsubo syndrome; LV = left ventricle; AHRQ = Agency for Healthcare Research and Quality; DPC = Diagnosis procedure combination; C = Circadian; W = Weekly; S = Seasonal; NR = Not reported.

* Data not included in the analyses (not extractable)

Moreover, for each (a) period of the day, (b) day of the week, (c) season with the highest pooled TTS rates, we estimated the expected number of TTS that could occur, in the absence of variation, using the average number of events in the remaining periods/days/seasons. The excess of events, as the difference between the observed and the expected TTS cases, was estimated and for each pattern of analysis, the relative risk of TTS as the ratio between the observed and expected number of events, with 95% Confidence Intervals (CI) was computed. 95% CIs were computed according to the simple asymptotic method without continuity correction described by Vollset.[13] Finally, for each pattern of analysis, the attributable risk (AR), and the population attributable risk (PAR) were assessed, the first defined as the ratio between the excess of TTS cases for each period/day/season and the observed number of events in the same time pattern, the second as the ratio between the excess of TTS cases for each period/day/season and the observed number of events throughout the entire day/week/year.[14-16]

All analyses were carried out using Stata, version 13.1 (Stata Corp., College Station, TX, 2013).

Results

Characteristics of the included studies and methodological quality

Of the 4257 papers initially retrieved, 20 studies (including 64,567 subjects) met the selection criteria and were included in the analyses[7,9,10,12,17-32] (Table 1). All cohort studies were prospective[23,28] or retrospective data collection, analyzing data from national- or county-level registries of pathologies[25,27,29,32] or hospital discharge abstracts. The studies were published from 2006 onwards, seven were performed in Europe,[7,9,18,21,23,26,30] six in the US,[10,20,22,24,25,32] seven between Asia (Japan or Korea),[12,19,27,29,31] or Australia/New Zealand.[17,28] The width of the sample size largely varied across studies, ranging from 32 to 41,000, with two studies enrolling >10,000 individuals. The proportion of females varied between 62% and 98%, and it was not reported in three studies.[22,23,25]

The quality assessment of the included studies are summarized in S-Table 1. The excluded studies, and reasons for the exclusion were summarized in S-Table 2. Eighteen studies adequately selected the cohort of patients and ascertained the exposure[10,22] (selection category items), and addressed the three items referred to outcome assessment and follow-up (length and missing data). The comparability of subjects was adequately assessed in seven studies.[19,24,26,28,29,30,32]

Table 2

Proportion meta-analysis: (a) circadian, (b) weekly, and (c) seasonal variations in the timing of Takotsubo syndrome (TTS) onset. Pooled rates of TTS were computed: (a) for each period of the day (morning: from 6am to 12am; afternoon: from 12am to 6pm; evening: from 6pm to 12pm; night: from 12pm to 6am); (b) for each day of the week; (c) for each season of the year. All analyses were performed either overall and, when possible, stratified by gender and stressor pattern.

	Overall Pooled % (95% CI)	Males Pooled % (95% CI)	Females Pooled % (95% CI)	Physical, stressors Pooled % (95% CI)	Psychological, stressors Pooled % (95% CI)	Idiopathic* Pooled % (95% CI)
A. Circadian variation						
- *N. studies (sample), ref.*	8 (853) [3, 6, 8, 16, 18, 21, 27, 28]			2 (141) [8, 21]	2 (84) [8, 21]	2 (46) [8, 21]
- Morning (6am-12am)	34.0 (28.6-39.6)	–	–	37.6 (29.7-45.8)	17.6 (9.9-26.8)	47.4 (32.8-62.2)
- Afternoon (12am-6pm)	32.1 (28.5-35.8)	–	–	29.7 (22.4-37.6)	35.4 (25.3-46.1)	34.4 (21.0-49.1)
- Evening (6pm-12pm)	21.7 (19.0-24.6)	–	–	22.7 (16.0-30.0)	21.7 (13.3-31.4)	10.5 (2.7-21.7)
- Night (12pm-6am)	12.7 (10.5-15.1)	–	–	9.8 (5.3-15.4)	22.1 (13.6-31.8)	3.6 (0.0-12.0)
B. Weekly variation						
- *N. studies (sample), ref.*	4 (549) [5, 8, 21, 27]	2 (44) [5, 8]	2 (105) [6,12]			
- Monday	17.3 (11.7-23.7)	31.2 (17.6-46.5)	22.4 (16.9-28.4)	–	–	–
- Tuesday	18.4 (15.2-21.7)	17.3 (6.6-30.9)	14.6 (10.0-19.8)	–	–	–
- Wednesday	17.2 (14.0-20.7)	15.0 (5.0-28.1)	17.5 (12.6-23.1)	–	–	–
- Thursday	13.0 (10.3-16.0)	7.2 (0.5-18.1)	16.5 (11.6-21.9)	–	–	–
- Friday	10.6 (8.2-13.4)	10.3 (2.0-22.2)	9.1 (5.5-13.6)	–	–	–
- Saturday	10.8 (6.0-16.8)	0.0 (0.0-5.4)	7.7 (4.4-11.9)	–	–	–
- Sunday	11.4 (8.8-14.2)	10.3 (2.0-22.2)	11.0 (7.0-15.7)	–	–	–
C. Seasonal variation						
- *N. studies (sample), ref.*	17 (64,167) [3, 6, 8, 14, 15, 17-27, 29]	3 (8411) [8, 24, 29]	3 (37,862) [8, 24, 29]	2 (178) [8, 25]	2 (136) [12,16]	2 (83) [12,16]
- Spring	22.0 (20.2-23.9)	24.2 (21.4-27.1)	21.8 (18.6-25.1)	17.9 (12.5-24.0)	28.9 (21.3-37.0)	21.5 (13.1-31.2)
- Summer	27.9 (25.9-29.9)	27.9 (22.5-33.6)	30.3 (25.6-35.2)	36.5 (29.5-43.7)	29.8 (22.2-38.0)	28.6 (19.1-39.0)
- Autumn	25.6 (24.0-27.2)	25.7 (24.8-26.6)	26.7 (23.1-30.5)	24.2 (18.1-30.8)	25.8 (18.6-33.8)	31.2 (21.5-41.8)
- Winter	21.7 (20.1-23.3)	22.9 (19.8-26.1)	21.4 (17.6-25.4)	21.3 (15.6-27.7)	13.4 (7.9-19.9)	17.9 (10.1-27.2)

CI = Confidence Interval

* No triggering stressors could be identified

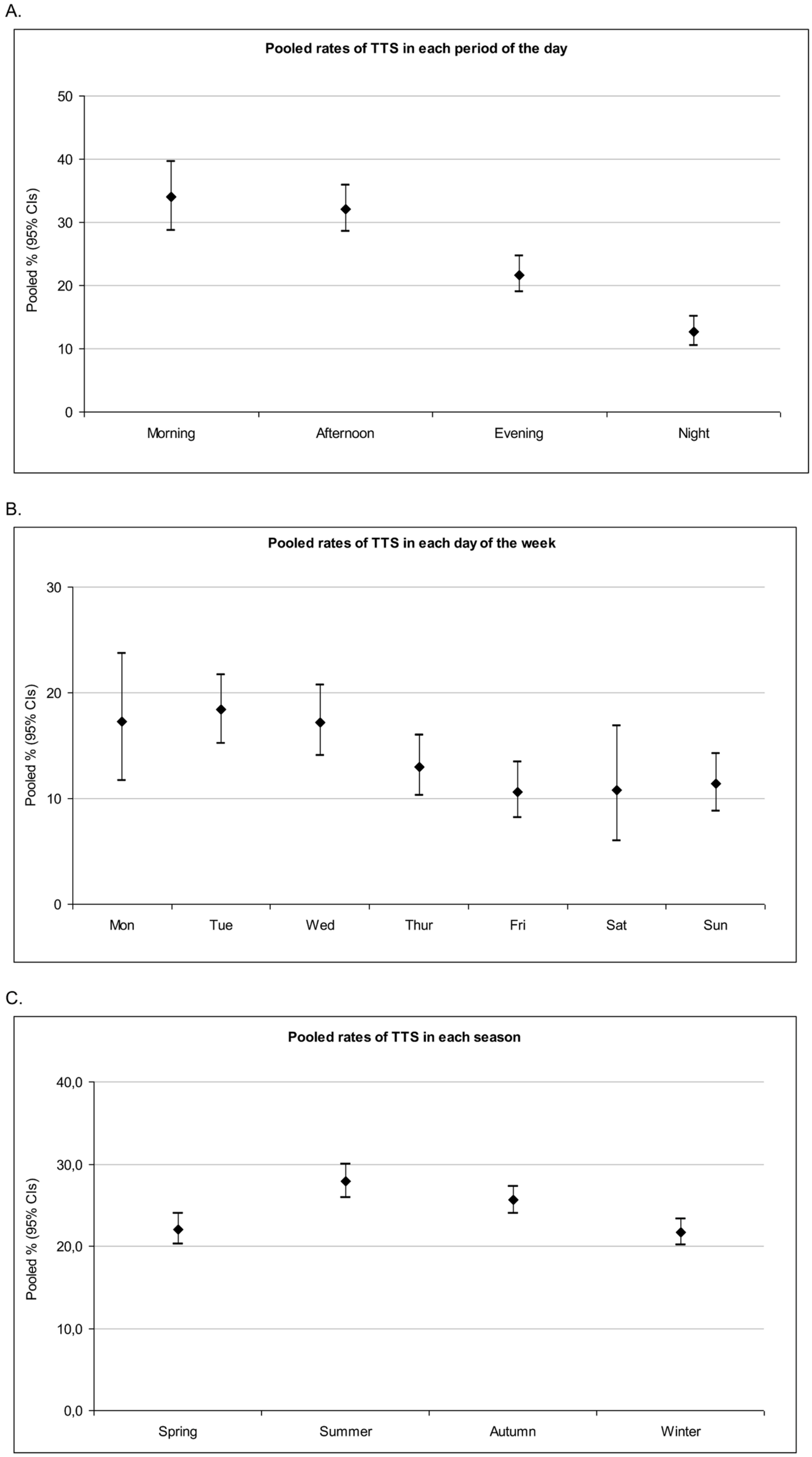

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Fig. 2. Pooled rates of Takotsubo syndrome (TTS) onset, and 95% CIs, occurring: (a) in each period of the day; (b) in each day of the week; (c) in each season.

Circadian, weekly and seasonal TTS patterns

A total of eight studies and 853 subjects were included in the proportion meta-analyses assessing the circadian variation of the pooled rates of TTS. Overall, a decreasing pattern was observed shifting from the morning to the night (pooled TTS rates: 34.0%; 32.1%; 21.7%; 12.7% in the morning, afternoon, evening and night, respectively; Table 2, Fig. 2). The same pattern was observed when the analyses were stratified by type of preceding stressful factor or event, considering physical stressors (pooled rates in the morning and night: 37.6% and 9.8%, respectively), and also in case no stressful factor or event could be identified. When analyzing psychological stressors, the peak of pooled TTS was observed in the afternoon (35.4%), with a later decline, up to 22.1% in the night.

In the analyses observing the weekly variation of TTS in the overall population (4 studies and 459 individuals), the pooled rates peaked on Monday and Tuesday (17.3% and 18.4%), then declined during the week, reaching the lowest rates on Friday and Saturdays (10.6% and 10.8%, respectively). An almost identical pattern was observed when the analyses were stratified by sex, with the highest

Table 3
a-c. Circadian, weekly and seasonal chronobiological patterns of Takotsubo syndrome (TTS). Observed and expected number of TTS, excess number of events, risk ratios (RR), attributable risk (AR) and population attributable risk (PAR) were computed for the (a) morning, (b) Monday, and (c) summer peaks of TTS onset, and for each study and overall.

a. Circadian pattern (morning peak of TTS onset)

First author	Year	Total n. TTS	N. obs. morning	N. exp. morning	N. excess	RR	95% CI	AR %	PAR %
Kurisu[19]	2007	37	15	7	8	2.05	1.58-2.51	51.1	20.7
Citro[7]	2009	79	32	16	16	2.04	1.73-2.36	51.0	20.7
Mansecal[22]	2010	51	22	10	12	2.28	1.86-2.69	56.1	24.2
Sharkey[24]	2012	134	34	33	1	1.02	0.85-1.19	2.0	0.5
Nascimento[10]	2013	50	19	10	9	1.85	1.47-2.22	45.8	17.4
Song[12]	2013	137	56	27	29	2.07	1.83-2.32	51.8	21.2
El-Battrawy[30]	2021	114	29	28	1	1.02	0.84-1.17	2.3	0.6
Yoshizawa[31]	2021	251	72	60	12	1.21	1.07-1.31	17.1	4.9
Overall		**853**	**279**	**191**	**88**	**1.46**	**1.38-1.54**	**31.4**	**10.3**

b. Weekly pattern (Monday peak of TTS onset)

First author	Year	Total n. TTS	N. obs. Monday	N. exp. Monday	N. excess	RR	95% CI	AR %	PAR %
Manfredini[9]	2010	112	23	15	8	1.55	1.32-1.78	35.5	7.3
Sharkey[24]	2012	186	23	27	-4	0.85	0.71-0.98	–	–
Song[12]	2013	137	34	17	17	1.98	1.74-2.22	49.5	12.3
El-Battrawy[30]	2021	114	15	17	-2	0.91	0.73-1.08	–	–
Overall		**549**	**95**	**76**	**19**	**1.26**	**1.16-1.35**	**20.3**	**3.5**

c. Seasonal pattern (summer peak of TTS onset)

First author	Year	Total n. TTS	N. obs. summer	N. exp. summer	N. excess	RR	95% CI	AR %	PAR %
Abdulla[17]	2006	35	11	8	3	1.38	0.99-1.76	27.3	8.6
Hertting[18]	2006	32	8	8	0	1.00	0.65-1.35	0.0	0.0
Citro[7]	2009	88	51	12	39	4.14	3.71-4.56	75.8	43.9
Regnante[20]	2009	59	28	10	18	2.71	2.29-3.13	63.1	29.9
Mansecal[21]	2010	51	6	15	-9	0.40	0.23-0.57	–	–
Summers[22]	2010	186	49	46	3	1.07	0.92-1.22	6.8	1.8
Parodi[23]	2011	116	32	28	4	1.14	0.95-1.34	12.5	3.4
Sharkey[24]	2012	186	44	47	-3	0.93	0.79-1.07	–	–
Nascimento[10]	2013	50	16	11	5	1.41	1.08-1.74	29.2	9.3
Song[12]	2013	137	53	28	25	1.89	1.66-2.12	47.2	18.2
Aryal[25]	2014	10,989	2928	2687	241	1.09	1.07-1.11	8.2	2.2
Novo[26]	2016	85	23	21	2	1.11	0.89-1.34	10.1	2.7
Isogai[27]	2017	4306	1243	1021	222	1.22	1.18-1.25	17.9	5.2
Looi[28]	2018	260	77	61	16	1.26	1.13-1.40	20.8	6.2
Desai[32]	2020	41,830	10,450	10,460	-10	1.00	0.99-1.01	–	0.0
Kanaoka[29]	2020	5643	1519	1375	144	1.10	1.08-1.13	9.5	2.6
El-Battrawy[30]	2021	114	26	29	-3	0.89	0.71-1.06	–	–
Overall		**64,167**	**16,564**	**15,868**	**696**	**1.04**	**1.04-1.05**	**4.2**	**1.1**

Obs. = Observed; Exp = Expected; AR = Attributable risk; PAR = Population attributable risk; CI = confidence Interval. N. excess = excess number of events occurring in the morning/on Monday/in summer; N. expected = expected number of events occurring in the morning/on Monday/in summer based on the average number of TTS occurring in the other time periods; RR = N. obs./N. exp.; AR% = % events occurring in the morning/on Monday/in summer that are due to the excess during the considered period (e.g. for the overall circadian pattern analysis AR%=(75/178)*100); PAR % = % of all events throughout the day/week/year due to the morning/Monday/summer excess (e.g. for the overall circadian pattern analysis PAR %=(75/488)*100).

rates on Monday and the lowest in the weekends both among males and females (Fig. S1-S15).

In the analyses assessing the seasonal variation of TTS, the pooled rates reached the highest values on summer, and the lowest in winter, both considering the overall population (27.9% versus 21.7% in summer and winter, respectively) and in all the stratified meta-analyses.

Table 3 (a-c) shows the observed-versus-expected number of TTS for each pattern. In the analyses considering the circadian pattern, there were a total of 279 TTS reported in the morning, between 6:00 am and 12:00 am, compared with 191 expected, based upon the TTS rates registered during the remaining 18 hours of the day (+88 TTS excess). Thus, the morning peak of TTS accounted for almost 33% of all the registered events, with a RR of 1.46 (95% CI: 1.38-1.54; AR 31.4%; PAR 10.3%) (Table 3 a). Similarly, when considering the studies providing the data for the analysis of the weekly and the seasonal variations, there were observed-to-expected cases in excess in both patterns, and the corresponding RRs and 95% CIs were always above 1: 1.26 (1.16-1.35) in the week-based analyses and 1.04 (1.04-1.05) in the season-based analyses (Table 3 b/c).

Discussion

Chronobiology is a science aimed to study biological rhythms. Biological rhythms may be divided into 3 main types: (1) ultradian (period <24 hours [eg, hours, minutes, or even seconds]), (2) circadian (period of approximately 24 hours), and (3) infradian (period >24 hours [eg, days, weeks, or months]). In this regard cardiovascular emergencies, such as acute myocardial infarction, stroke, acute aortic dissection, show distinct chronobiological patterns in their onset, with higher frequency in the morning hours and in the winter.[1,33]

The present comprehensive and updated systematic review and meta-analysis about chronobiological patterns of TTS onset, highlights a peak in the morning and on the first two days of the week, declining during the week. Interestingly, the quantitative analysis stratified for stressful factors and for sex confirmed the same pattern. In contrast to acute myocardial infarction and aortic dissection, TTS seemed more frequent during summer with the lowest values of pooled rates in winter.

As TTS pathophysiology is concerned, several underlying mechanisms have been proposed, mainly (i) catecholamine-mediated plaque rupture, (ii) intraventricular obstruction due to an excessive sympathetic stimulation in individuals with smaller ventricles and localized septal thickening, (iii) microvascular dysfunction and/or direct myocyte effects with catecholamine induced myocardial stunning.[34-40] In this regard, the high proportion of TTS onset in the morning may be in part explained by the circadian periodicity of catecholamines.[1,37] In addition previous investigators have demonstrated sympathetic nervous system hyperactivity during TTS onset along with higher norepinephrine and dopamine levels during mental stress and exercise.[38-40] In fact, TTS acute episodes are frequently triggered by sudden, unexpected stress or major physical illness or trauma.[35,36] Furthermore intravenous catecholamines infusion may precipitate TTS in humans and in animal models.[35] On the other hand no clear elucidation can be given to the prevalent onset on Monday and Tuesday and the summer preference[1,37]

Finally, it should be underscored, publication bias may have influenced the results of the present report. However, this was a meta-analysis of proportions, with no direct comparisons, thus avoiding the typical bias deriving from the lower publication rate of non-significant results.[41]

Conclusion

TTS onset was more frequent in the morning and on the first two days of the week, declining its rate during the week. Furthermore, a summer preference of TTS onset was found. This chronobiological patterns didn't change if stressful factors or sex were considered. Further studies are needed to fully understand the underlying pathophysiological mechanisms in order to tailor relative management and preventive strategies.

CRediT authorship contribution statement

Andreina Carbone: Writing – review & editing. **Maria Elena Flacco:** Writing – original draft, Formal analysis. **Lamberto Manzoli:** Validation, Formal analysis. **Nicola Lamberti:** Data curation. **Filippo Pigazzani:** Data curation. **Salvatore Rega:** Data curation. **Serena Migliarino:** Data curation. **Francesco Ferrara:** Writing – review & editing. **Rodolfo Citro:** Writing – review & editing. **Roberto Manfredini:** Supervision, Methodology, Conceptualization. **Eduardo Bossone:** Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding sources

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cpcardiol.2024.102804.

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