Sex-related differences and chronobiology of ST-elevation myocardial infarction: findings from a single hub center in Italy

A. RIZZA[1], A. DE GIORGI[2], F. NEGRO[3], B. BOARI[2], C. PALMIERI[1], S. BERTI[1], R. MANFREDINI[2,3,4]

[1]Cardiology Unit, Ospedale del Cuore, Fondazione Toscana "G. Monasterio", Massa, Italy
[2]Clinica Medica Unit, Azienda Ospedaliero-Universitaria 'S. Anna', Ferrara, Italy
[3]Cardiology Division, Pisa University Hospital, Pisa, Italy
[4]Department of Medical Sciences, University Center for Studies on Gender Medicine, University of Ferrara, Ferrara, Italy

Antonio Rizza and Alfredo De Giorgi contributed equally as first authors

Abstract. – OBJECTIVE: Type I acute myocardial infarction (AMI) is a life-threatening condition. Time of event and rescue procedures, and sex-specific differences may play a crucial role. We aimed to investigate chronobiological patterns and sex-specific differences in a cohort of AMI patients referred to a single hub center in Italy.

PATIENTS AND METHODS: We considered all patients consecutively admitted for AMI (STEMI) to the Hospital of the Heart, in Massa, Tuscany (a region of Italy), between 2006 to 2018, who underwent interventional procedures. Sex, age, time of hospital admission, outcome (discharged alive/deceased), main comorbidities, and time between symptom onset and emergency medical service (EMS) activation, were analyzed. Chronobiologic analysis was applied according to hour of day, month, and season of the year.

RESULTS: Overall 2,522 patients (mean age 64.6±13.1 years, 73% males) were considered. In-hospital death (IHM) occurred in 96 subjects (3.8%). At univariate analysis, deceased subjects were more likely to be female, older, with longer wait for EMS activation and with interventional procedures during night-time. The multivariate analysis identified female sex, age, history of ischemic heart disease, and night-time interventional procedure as independently associated factors to IHM. Chronobiologic analysis showed a pattern with a main morning peak for total sample, males, and females (p=0.00027; p=0.0006); p=0.0121, respectively). Events showed a higher peak in summer, with no differences by sex, but IHM was higher in winter. Females showed a higher delay for EMS activation, compared to males (p<0.001), but with no effects on prognosis. On the contrary, males with a delay showed higher mortality.

CONCLUSIONS: Great effort should be spent to reduce patient-related delays in interventional procedures, being this issue crucial in both sexes.

Key Words:
Acute myocardial infarction, Sex, Chronobiology, Circadian rhythm, Seasons, Acute coronary syndrome, Coronary artery disease, Percutaneous coronary intervention, Time of procedure.

Introduction

Acute myocardial infarction (AMI) is defined as acute myocardial injury in the setting of evidence of myocardial ischemia[1]. According to the fourth universal definition, type I AMI occurs when myocardial blood supply is acutely reduced by thrombotic obstruction of the lumen of an epicardial coronary artery because of atherosclerotic plaque rupture or erosion[1]. Patients presenting with AMI and ST-segment elevation in at least two consecutive ECG leads are usually designated as ST-elevation myocardial infarction (STEMI)[2]. In this clinical condition, urgent invasive coronary angiography and revascularization are mandatory. Although in most cases a complete obstruction of coronary lumen can be observed, STEMI can also occur in the absence of coronary artery disease[2]. Although in the last two decades STEMI incidence has reduced in both American and European Countries (43-144 cases per 100,000 subjects per year), ischemic myocardial disease still represents the most common cause of death worldwide[2]. STEMI affects generally younger people and is more common in men than in women[3], and mortality is influenced by many factors, such as advanced age, Killip class, time delay to treatment, presence of emergency

Corresponding Author: Alfredo De Giorgi, MD; e-mail: degiorgialfredo@libero.it

medical system-based STEMI networks, treatment strategy, and patients' comorbidity (history of AMI, diabetes mellitus, renal failure, number of diseased coronary arteries, and left ventricular ejection fraction)[4]. Interestingly, some studies[5] recently noted that a high body mass index (BMI) could benefit patients with coronary heart disease (CHD), and a lower incidence of long-term major adverse cardiovascular events (MACE) has been reported in patients with high BMI, especially recurrent AMI, in patients with STEMI undergoing percutaneous coronary intervention (PCI). The in-hospital mortality (IHM) remains between 4 and 12% in unselected patients with STEMI in the national registries of the European countries[4]. Timely corresponding treatments and reduction of reperfusion damage are of great significance for STEMI patients[6]. Thus, time represents a crucial point in medicine, in particular for – although not only limited to – cardiovascular diseases. It is known that biological rhythms exist at any level of all living organisms and, according to their cycle length, are classified into a) circadian (from the Latin circa-dies, period of ~24 hours), b) ultradian (period <24 hours), and c) infradian rhythms (period >24 hours, e.g., seasons, months, or weeks). Also, the onset of many acute cardiovascular diseases, including stroke, rupture or dissection of aortic aneurysms, pulmonary embolism, and Takotsubo syndrome, is characterized by evident rhythmic temporal patterns, as reported also by several studies[7-14] from our group. As for AMI, after the first milestone study by Muller et al[15], many studies[16] worldwide provided robust confirmation of the existence of a morning peak of onset. Interestingly, it has been observed that morning preference of AMI may also have effects on outcome[17]. Diurnal variations in multiple biologic functions, such as assumption of an upright posture associated with increased platelet aggregability, changes in blood clotting and fibrinolysis, may be potentially active triggering factors[18], and variations in sympathetic tone, catecholamine secretion, and blood pressure are also implicated[19]. Moreover, a series of studies[20-22] reported differences regarding seasonal patterns of onset of AMI, characterized by a winter peak and a summer trough. Interestingly, Daylight-Saving Time transitions from winter to spring (and not vice versa) has been associated with more AMI and stroke episodes, especially on Mondays[23-25]. In fact, Monday is considered as the stressful day of the week, being also characterized by a higher frequency of strokes and Takotsubo syndrome events[26,27].

The aim of the present study was to investigate the chronobiological patterns and possible sex-specific differences in a single-center cohort of type 1 STEMI patients referred to a hub center of the Tuscany region in Italy.

Patients and Methods

Study Design and Sample

This retrospective cohort study was conducted in agreement with the declaration of Helsinki of 1975, revised in 2013. In order to maintain data anonymity and confidentiality, patient identifiers were cancelled before data analysis, deleting the possibility of identification of subjects, either in this paper or in the database. Ethical committee approval was not necessary because the study was managed in agreement with the existent Italian disposition-by-law (G.U. n.76, 31 March 2008). The study included all patients consecutively admitted for AMI (STEMI) to the "Cath lab for STEMI" of the "Hospital of the Heart - G. Pasquinucci" in Massa, Italy, between January 2006 to December 2018, who underwent coronary angiography and coronary stent implantation. The "Hospital of the Heart" is a highly specialized hospital fully oriented to the diagnosis and treatment of cardiovascular diseases and represents the referral hub center for the 10% of all cases of STEMI of the Tuscany region in Italy [https://www.ars.toscana.it]. The city of Massa (66,423 inhabitants) is the capital of the province of Massa-Carrara (194,878 inhabitants) and is located at just few kilometers from the Tyrrhenian Sea. The climate is Mediterranean and particularly mild, without high heat and cold peaks in summer and winter: the average temperature ranges from 7.25°C in January to 28°C in July. Due to these favorable climatic conditions, during summer months the overall population of this area increases up to 25% (more than 900,000 people compared to the 3.5 millions of local population) [https://www.ars.toscana.it].

The diagnosis of STEMI was based on the most recent guidelines, considering typical clinical symptoms consistent with myocardial ischemia (i.e., persistent chest pain) and the electrocardiographic signs[2]. ST-segment elevation (measured at the J-point) was considered suggestive of ongoing coronary artery acute occlusion in the presence of at least two contiguous leads with ST-segment elevation 2.5 mm in men aged <40 years, 2 mm in men aged ≥40 years, or 1.5 mm in women in leads V2-V3 and/or 1 mm in the other leads or recent onset left bundle branch block[1]. Moreover, the following clinical parameters were also considered: sex, age, time and date of hospital admission, outcome (discharged alive/deceased), length of stay, and the presence of principal cardiovascular comorbidities, such as history of hypertension, diabetes mellitus, and dyslipidemia, active smoking habit, personal and familiar history of cardiovascular disease. Again, the time elapsed between the chest pain onset and the first medical contact following the emergency medical service (EMS) activation, was recorded.

Statistical Analysis

The data are expressed as absolute numbers, percentages, and mean ± standard deviation (SD). Descriptive analysis was carried out and the main outcome was in-hospital mortality (IHM). The univariate analysis was conducted using the χ^2, Student-*t* tests, Mann-Whitney test as appropriate in order to evaluate the conditions related to IHM. Moreover, in order to represent data aiming at classifying comorbidities, a hierarchical clustering (cluster tree) was built for obtaining a dendrogram[28], where each group (or "node") links to two or more successor groups.

Independent parameters associated to IHM were analyzed employing logistic regression analysis, taking as the independent variables those that showed a significant difference between survivors and deceased subjects at the univariate analysis. Odds ratios (ORs) and 95% confidence intervals (95% CI) were reported. All *p*-values were 2-tailed, and *p*-value <0.05 was considered significant. Statistical Product and Service Solution (SPSS) 23.0 for Windows (IBM Corp., Armonk, NY, USA) was used for the statistical analyses.

Moreover, the time of each event occurrence was tabulated, and the chronobiological analysis was carried out based on time of STEMI onset. Partial Fourier analysis to the time series data using Cosinor software (Time Series Analysis-Cosinor, Esvres, France) was performed for testing chronobiological pattern. The Cosinor method allows to identify rhythmic patterns, i.e., reproducible for each considered period, and the software permits the selection of the harmonic, or combination thereof, that best explain the variance of data. Acrophase (peak time of rhythmic change) and peak and trough times of the overall best fitted curve (times of occurrence of the absolute maximum and minimum) were calculated. Cosinor analysis was applied to hour of day, to month and to season. For circadian analysis, the clock time of each event was categorized by hour during the 24 h and into one of four 6 h intervals. Day of admission was then categorized into four 3-month intervals (spring: March 21-June 20; summer: June 21-September 22; autumn: September 23- December 20; winter: December 21-March 20) and into twelve 1-month intervals, for seasonal and monthly analysis, respectively. All these analyses were performed in the total population, and male and female subgroups. Significance levels were set at $p<0.05$.

Finally, we plotted the observed/expected ratio during the study period. The observed number of STEMI cases per month were calculated as the monthly numbers of events over the whole study period. The expected number of cases per month was obtained by dividing the average number of patients per year by 365.25, multiplying the results by the number of days each month, and considering 28.25 days for February. The STEMI observed/expected ratio of events was thus calculated. We also evaluated the waiting time between the onset of symptoms and the first medical contact.

Results

A total of 2,522 patients (72.8% males, mean age 64.6 ± 13.1 years) were included in the study. In total 96 patients died during hospitalization (IHM=3.8%). The univariate analysis (Table I) showed that the deceased subjects were more likely to be females, older, to undergo interventional procedure during night-time, and with a longer wait for activation the medical emergency service (167.1 ± 209.8 *vs.* 138.3 ± 198 minutes). Among the comorbidities, diabetes and personal history of cardiovascular disease were associated with higher mortality. Table II shows the different comorbidity distribution by sex, and the dendrogram (Figure 1) shows the associations between such comorbidities. The multivariate analysis (Table III) identifies female sex, age, history of ischemic heart disease, and night-time interventional procedure as independently associated factors to IHM.

A significant circadian rhythm was identified for the entire study population (cosinor analysis: p=0.00027, observed/expected ratio analysis: $p<0.001$) with a bimodal pattern, characterized by a main peak in the morning (09:24), and a secondary one in the afternoon (15:38) (Figure 2). The same pattern was confirmed in subgroups by sex (cosinor analysis: p=0.00061 and p=0.01212, for males and females, respectively).

Table I. Demographic, temporal patterns, history, and comorbidities of survivors and deceased subjects.

	Total patients (n = 2,522)	Survivors (n = 2,426)	Deceased (n = 96)	p
Male, n (%)	1,835 (72.8%)	1,791 (73.8%)	44 (45.8%)	<0.001[#]
Female, n (%)	687 (27.2%)	635 (26.2%)	52 (54.1%)	
Age (years)	64.6±13.1	64.2±13.1	75.2±10.9	<0.001[+]
Waiting time for rescue (min)	139.4±194.6	138.3±198	167.1±209.8	0.045[§]
Spring, n (%)	656 (26%)	632 (26.1%)	24 (25%)	NS[#]
Summer, n (%)	709 (28.1%)	685 (28.2%)	24 (25%)	
Fall, n (%)	619 (24.5%)	597 (24.6%)	22 (22.9%)	
Winter, n (%)	538 (21.3%)	512 (21.1%)	26 (27.1%)	
Diabetes mellitus, n (%)	511 (20.3%)	483 (19.9%)	28 (29.2%)	0.027[#]
Dyslipidemia, n (%)	794 (31.5%)	766 (31.6%)	28 (29.2%)	NS[#]
Hypertension, n (%)	1,453 (57.6%)	1,394 (57.5%)	59 (61.5%)	NS[#]
Active smoking habit, n (%)	1,018 (40.4%)	1,003 (41.3%)	15 (15.6%)	<0.001[#]
Personal history of cardiovascular disease, n (%)	307 (12.2%)	287 (11.8%)	20 (20.8%)	0.008[#]
Familiar history of cardiovascular disease, n (%)	661 (26.2%)	650 (26.8%)	11 (11.5%)	0.001[#]
n° of comorbidity	1.62±1.05	1.62±1.04	1.56±1.17	NS[§]

[#]: χ^2 test; +: *t*-test; [§]: Mann-Whitney test.

Table II. Age, history, comorbidities, and waiting time for rescue: differences by sex.

	Male (n = 1,835)	Female (n = 687)	p
Age (years)	62 ± 12.3	71.5 ± 12.9	< 0.001[+]
Diabetes mellitus, n (%)	352 (19.2%)	159 (23.1%)	0.028[#]
Dislipidemia, n (%)	582 (31.7%)	212 (30.9%)	NS[#]
Hypertension, n (%)	998 (54.4%)	455 (66.2%)	< 0.001[#]
Active smoking habit, n (%)	857 (46.7%)	161 (23.4%)	< 0.001[#]
Personal history of cardiovascular disease, n (%)	257 (14%)	50 (7.3%)	< 0.001[#]
Familiar history of cardiovascular disease, n (%)	526 (28.7%)	135 (19.7%)	< 0.001[#]
Number of comorbidities	1.66±1.07	1.51±0.97	0.008[§]
Waiting time for rescue (min)	134.4±193	152.7±198.6	< 0.001[§]

#: χ^2 test; +: *t*-test; [§]: Mann-Whitney test.

As for the monthly pattern (Figure 3) the highest peak occurred during summer months (July-August) and the lowest during the colder months (January-February), a model confirmed either by the cosinor analysis (*p*=0.00331), and the observed/expected ratio (*p*=0.045). Similar results were obtained analysing seasonality (*p*<0.001). The same pattern was confirmed in subgroups by sex (cosinor analysis: *p*=0.00412 and *p*=0.00846, for males and females, respectively). On the other hand, data corrected for the observed/expected ratio did not reach the statistical significance level. Despite the higher incidence of STEMI during the summer months, IHM was higher during winter than summer period (4.8% *vs.* 3.4%, respectively) in the whole population, in males and in females (Figure 4). These data were confirmed also for the observed/expected ratio in the total population, males, and females (*p*=0.00081), *p*=0.05), *p*=0.01141, respectively).

Finally, we evaluated the timelines of the EMS activation. The waiting times between the onset of the symptom and the first medical contact increased progressively during the study period (Table IV). Females tended to delay the call to the EMS compared to males (152.7 ± 198.6 *vs.* 134.4 ± 193 min, *p*<0.001), with no effects on prognosis. On the contrary, males showing a delay in calling EMS showed higher mortality (Figure 5). There was no relationship between activation of EMS and seasonality (*p*=0.487).

Figure 1. Hierarchical clustering (cluster tree) showing a dendrogram where each group (or "node") links to two or more successor groups.

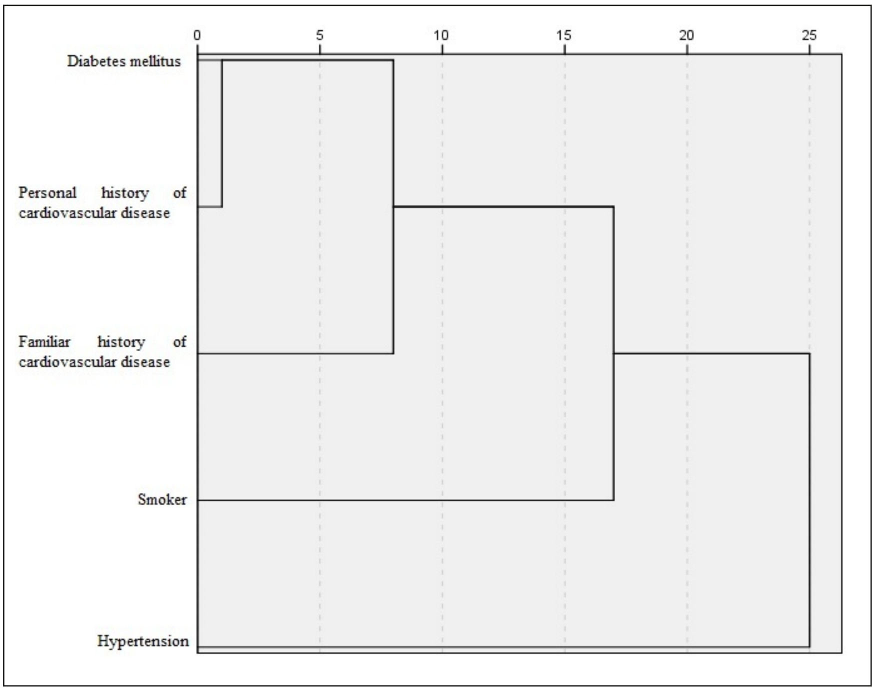

Table III. Regression analysis and factors independently associated to IHM.

	OR	95% C.I.	*p*
Female	1.879	1.185 - 2.978	0.007
Age	1.051	1.029 - 1.073	< 0.001
Personal history of cardiovascular disease	1.880	1.064 - 3.321	0.030

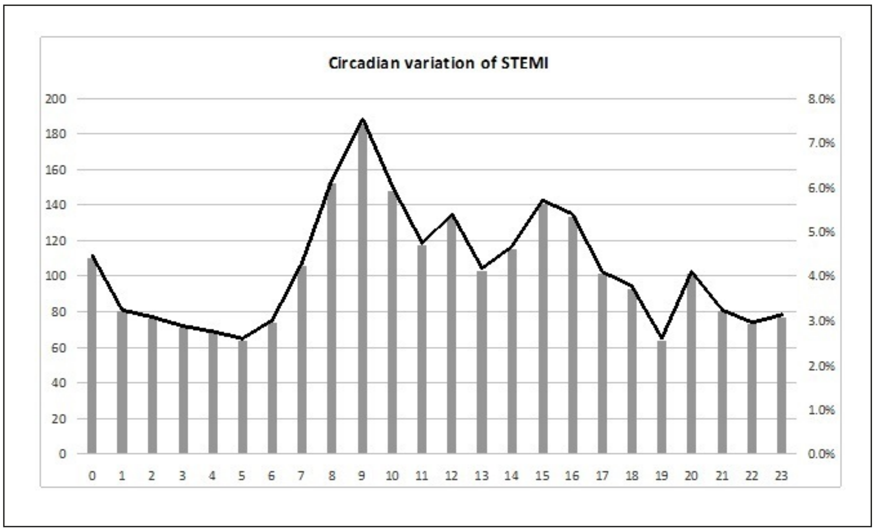

Figure 2. Circadian variation of STEMI (total population).

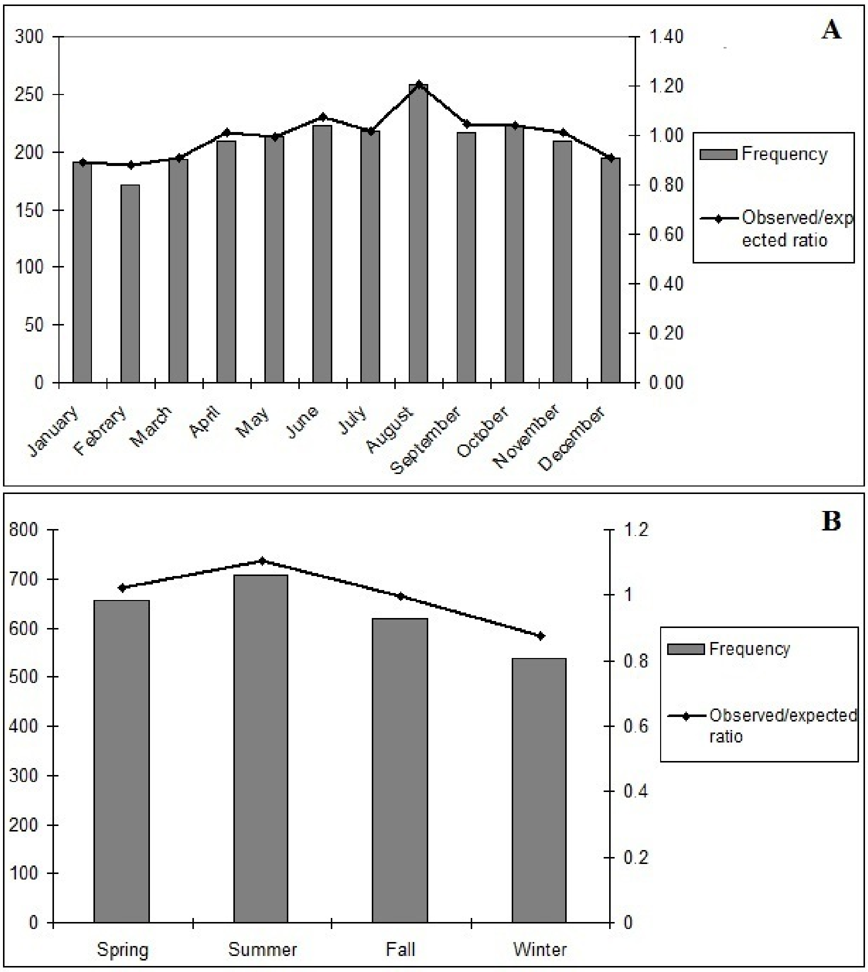

Figure 3. Circannual (**A**) and seasonal (**B**) variation of STEMI (total population).

Discussion

Although women live longer than men[29], cardiovascular disease is the leading cause of mortality in women, so that the American Heart Association a few years ago published a scientific statement specifically on acute myocardial infarction in women[30]. In fact, sex-specific differences exist in the presentation, pathophysiological mechanisms, and outcomes in patients with AMI[30]. For example, sex/gender (and age) have a value of diagnostic validity in the prediction models of unstable angina pectoris and NSTEMI[31], and social support and depressive symptoms may be predictors, respectively, of an increased risk of obstructive CAD and poor long-term function after coronary artery bypass grafting (CABG), in women[32,33]. The present study, conducted on a selected single hub center, shows some remarkable sex-specific differences. On one hand, on univariate analysis, IHM was significantly associated to female sex, age, night-time interventional procedure, and longer wait for emergency medical intervention. The multivariate analysis confirmed that female sex, age, history of ischemic heart disease, and night-time interventional procedures were all independently associated factors to IHM. If age and history of ischemic heart disease are established, classic risk factors, sex, off-hours procedure, and delay deserve some consideration. Moreover, the impact of comorbidities is important, and exhibits some differences between males and females.

Off-Hours and Effects on Cardiovascular Diseases

A couple of decades ago, Henriques et al[34] studied more than 1,700 consecutive patients with acute STEMI treated with primary angioplasty in Holland and evaluated the differences between duty hours (8 AM-6 PM) and off-hours (6 PM-8 AM). Although circadian patterns of symptom

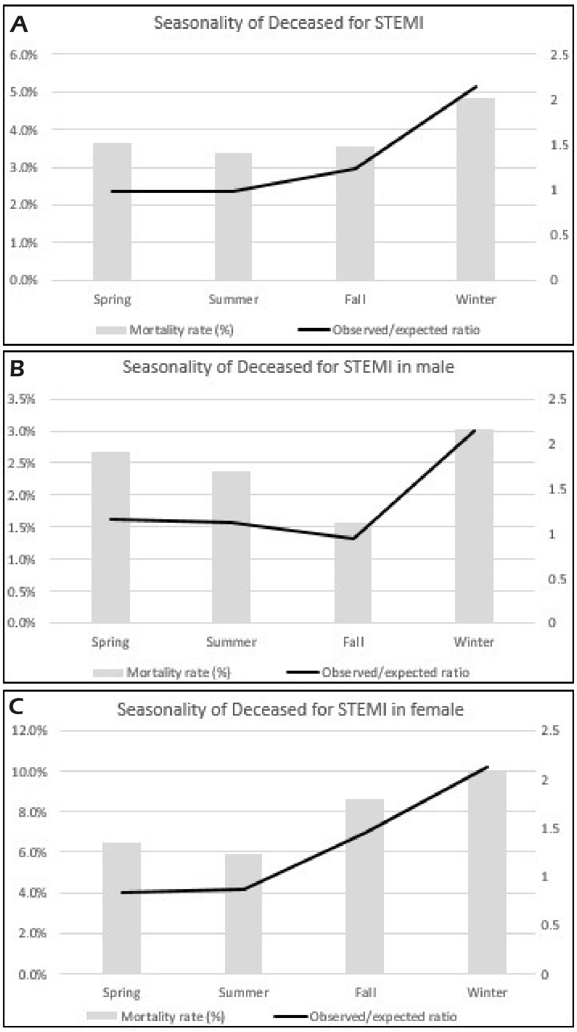

Figure 4. Seasonal variation of in-hospital mortality: (**A**) total population, (**B**) males, (**C**) females.

onset, hospital admission, and balloon inflation were similar, hospital admission during duty hours was associated with an angioplasty failure rate of 3.8%, compared with 6.9% during off-hours, (p<0.01). Moreover, also 30-day mortality was significantly lower for patients admitted during duty hours compared with off-hours (1.9% *vs*. 4.2%, respectively, p<0.01)[34]. Also, De Luca et al[35], in Holland, reported a significant relationship between time of treatment and clinical outcome in 1,549 consecutive STEMI patients undergoing primary angioplasty. In fact, patients treated between 4 and 8 AM showed the worst outcome in terms of myocardial perfusion, enzymatic infarct size, and 1-year mortality. A few years later, Glaser et al[36] evaluated 695 consecutive patients undergoing primary PCI in the National Heart, Lung, and Blood Institute Dynamic Registry, that were classified as occurring during routine-hours (7 AM-7 PM) or off-hours (7 PM-7 AM). Patients presenting at off-hours were more likely to present with cardiogenic shock and multivessel coronary artery disease, and procedural complications were more frequent in off-hours patients. In-hospital death, MI, and target vessel revascularization were significantly higher in off-hours patients (adjusted OR: 2.66, p=0.001), and differences in outcomes were worse even if the procedure was immediately successful (adjusted OR: 2.58, p=0.005)[36]. Again, Ofoma et al[37] reported a lower survival during off-hours also in their cohort of patients with in-hospital cardiac arrest. It is also possible that time of onset of acute cardiovascular syndromes and clinical outcome could be related[38]. A study conducted on approximately 2,000 consecutive acute coronary syndrome (ACS) admissions to a tertiary-care academic center in Michigan (MI, USA), evaluated the clinical variables of patients admitted on days *vs.* nights and weekdays (WD) *vs.* weekends (WE)[39]. There were significantly fewer ACS admissions than expected on nights and WE, but the proportion of patients with STEMI was 64% higher on WE and 31% higher on nights (p=0.022). This increased proportion with STEMI resulted in a greater proportion of ACS with AMI on WE (p=0.006) and nights (p=0.033)[39]. Very recently, a series of systematic reviews[40-42] and meta-analyses provided robust confirmation on this topic. Cortegiani et al[40] (40 observational studies, approx. 3 million patients) demonstrated as association between night/after-hours surgery and a higher risk of mortality (OR: 1.16). Wang et al[41] (10 cohort studies, more than 250,000 cases), found that night-time was associated with a lower survival after out-of-hospital cardiac arrest (OHCA). In fact, patients with night-time OHCA had significantly lower short-term survival compared to patients with daytime OHCA (OR: 1.20). Finally, Yu et al[42] (45 studies, more than 15 million patients) found that out-of-hour admission was associated with a significantly increased risk of both short- and long-term mortality for AMI (OR: 1.04 and 1.03, respectively).

Chronobiology: Circadian Aspects

It has been observed that emergency calls respect a circadian variation along the day, with the morning hours characterized by peak frequency of calls for cardiologic, respiratory, and neurologic disease, and afternoon higher frequency of calls for trauma, neoplastic diseases,

Table IV. Waiting time between onset of symptoms and first medical contact along the study period.

Year	Time (hours)
2006	1.45±1.38
2007	1.57±1.41
2008	1.98±1.94
2009	1.92±1.8
2010	1.9±2.24
2011	1.98±1.78
2012	1.83±2.54
2013	1.64±1.72
2014	2.99±4.35
2015	2.45±3.28
2016	3.46±4.51
2017	2.5±3.6
2018	3.79±5.75

and acute poisoning[43]. Also, the data from the present study, on a selected population of STEMI patients referring to a highly specialized center, show the existence of a bimodal pattern, with the highest peak in the morning and a secondary one in the early afternoon. These results are in agreement with recent observations on patients who underwent PCI[44]. Moreover, the lack of differences in subgroups by sex, provide further confirmation to the available data in literature. In fact, the analysis of 20 years of chronobiologic studies dealing with life-threatening acute cardiovascular diseases, observed that 44% of studies[45] provided separate analyses by sex, collecting 85% of total cases. Morning hours were confirmed as critical time of onset of AMI, sudden cardiac death, cardiac arrest, rupture or dissection of aortic aneurysms, and stroke, either in men or women[45]. The cardiovascular system is organized in a circadian manner, and defense mechanisms against acute events cannot provide the same degree of protection over the entire 24 hours. Gates of higher susceptibility to aggressive mechanisms exist, particularly in the morning and, to a lesser extent, in the late afternoon. Thus, when peaks of critical factors are aligned together at the same time, the risk of acute events becomes significantly elevated[18].

Chronobiology: Seasonal Aspects

Our data shows apparently contrasting results. On one hand, the highest peak of occurrence was observed during summer months, in both subgroups by sex. On the other, however, IHM was significantly higher during winter, for total cases and subgroups by sex. Most studies[20,22,46,47], have shown a winter preference for AMI onset others gave negative results[48]. However, also the type of infarction, MI with obstructive coronary artery disease (MI-CAD) and non-obstructive CAD (MINOCA), could be associated with different seasonal patterns. In fact, a study on 322,523 patients (35% female) from the National Cardiovascular Data Registry Acute Coronary Treatment Intervention Outcomes Network (ACTION) Registry-Get With the Guidelines, did not find any seasonal pattern of MI overall[49]. However, both men and women with MINOCA presented more often in the summer and fall while MI-CAD presentations were equally distributed across seasons. It is also possible that differences in monthly or seasonal admissions may depend

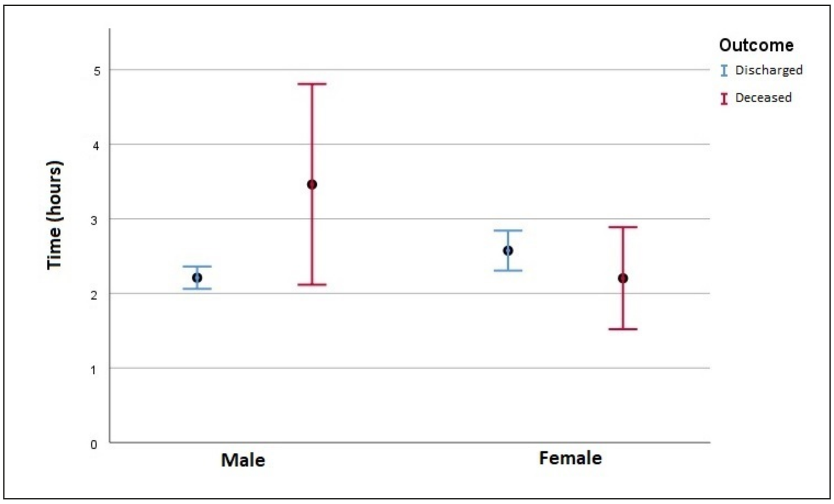

Figure 5. Time between onset of symptoms and first medical contact following the activation of the emergency medical service: sex difference and impact on outcome.

on variation of total population of a certain area. This could be the case of a hub hospital located in a nice sea site, where thousands of tourists every summer migrate from other regions, so that a greater number of procedures, such as coronary angiography, CABG and PCI are performed, due to the greater number of patients in the resort areas. The significant higher mortality in winter is in agreement with multiple observations in studies on millions of subjects[50,51]. Moreover, life-threatening complications after revascularization, such as ventricular fibrillation, cardiac arrest, heart failure, and reinfarction was higher in the colder months (autumn/winter) than in the warmer ones (spring/summer)[52]. The "cold stress" could increase the severity of an event rather than trigger its development[53-55]. However, the investigators from the Get With The Guidelines-Coronary Artery Disease database analyzed 82,971 consecutive AMI patients treated at 276 US centers, geographically divided into warmer southern and colder northern states[55]. AMI admissions showed a seasonal variation with higher peak in winter for all AMIs and NSTEMI, but not for STEMI, in which the seasonal variation was not significant. Moreover, the seasonal winter preference was observed in AMI patients in warmer southern states ($p<0.01$), but not in colder states[56]. Interestingly, such finding recalls the observation on a cohort of worldwide patients enrolled in the International Registry of Acute Aortic Dissection (IRAD), where the significantly higher incidence of acute aortic dissection events in winter was present in both cold and temperate climate settings[57]. Older patients with myocardial infarction have a reduced physiological reserve during winter, following a higher incidence of pulmonary inflammatory events due to low temperatures[53], and this could be one of the possible causes also of the winter increase of hospital admissions for heart failure, independent of subgroups by sex, age, major cardiovascular risk factors, and clinical outcome[58]. A study on a large cohort of STEMI in Canada found that, despite a higher incidence of STEMI in women during summer, significantly more women arrived at the hospital with cardiogenic during winter[59].

Delay to Interventional Procedure

Delays in treatment of AMI patients are related to increased morbidity and mortality, and identification of determinants of delay may help reduce time to treatment. Alnsasra et al[60] reviewed data on 3,658 patients with AMI. In patients with STEMI, independent determinants of delay included atypical chest pain, night presentation, and diabetes. In non-STEMI patients, independent determinants of delayed invasive approach were female sex, age >75 years, atypical chest pain, and renal failure[60]. In the present study, we did not find significant differences between seasons, but a significant increase was shown from 2006 to 2018. This trend represents a worrying, though not completely surprising if we remember the continuous need of mediatic campaigns aimed to raise the public awareness of "chest pain" especially in women. Women with AMI, compared with men, are less likely to receive guideline-indicated pharmacological (aspirin, $P2Y_{12}$ inhibitors, statins) and revascularization treatments (angiography, PCI)[61]. Moreover, sex-specific differences are evident for clinical outcomes as well. An Australian study[62] on 6,179 consecutive patients presenting with STEMI undergoing PCI, showed that females were older, had more co-morbidities, had longer median symptom-to-balloon times and longer median door-to-balloon times, and showed unadjusted in-hospital and 30-day mortality rates higher than men (8.8% *vs.* 6.2%, 9.8% *vs.* 6.9%; $p<0.001$). Sex-specific differences are also present regarding the delay in EMS activation especially in females, with confirmation in both European and extra-European countries[63-67]. The reasons are unknown, although it is possible that females could frequently suffer from atypical symptoms during the acute phase of AMI[2]. In our study, females showed a higher delay in EMS activation, but it was associated with a worse outcome only in males. In their recent meta-analysis study, Shah et al[68] confirmed that females had significantly longer delays to first medical contact (mean difference 42.5 min) and door-to-balloon time (mean difference 4.9 min). However, although females had a higher IHM rate, there was no correlation in relation to the EMS delay.

Limitations

This study has several limitations: (i) the retrospective design; (ii) data were collected in a single centre, with special attraction either as hub centre and being located in a tourist area with wide summer variability in the number of population, so that the results by season could not be generalizable; (iii) there were some differences among survivors and deceased, being the latter more likely to be older and with higher comorbidity burden; (iv) last but not least, information about medical treatment is missing.

Conclusions

The present study, conducted on a selected population of cases referring to a hub centre, confirmed the presence of the circadian variation of STEMI, characterized by a morning main peak of frequency. Despite a higher frequency of events in summer, possibly influenced by a population migration bias, IHM was significantly higher during winter months. Although no differences by sex were observed in these chronobiological patterns, sex-specific differences were found for waiting time for EMS (higher for females) and clinical outcomes (worst for males). Great effort should be spent to reduce patient-related delay in interventional procedures, being this issue crucial in both sexes.

Conflict of Interest

Authors have no conflict of interest to declare.

Acknowledgements

We thank Dr. Claudia Righini and Dr. Donato Bragatto, Biblioteca Interaziendale di Scienze della Salute, Ferrara, Italy, for their precious support.

Informed Consent

In order to maintain data anonymity and confidentiality, patient identifiers were cancelled before data analysis, deleting the possibility of identification of subjects, either in this paper or in the database.

Ethical Approval

This retrospective cohort study was conducted in agreement with the declaration of Helsinki of 1975, revised in 2013. The study was based on hospital data obtained consulting clinical records, and in agreement with the existent Italian disposition-by-law (G.U. n.76, 31 March 2008) ethical approval was not requested.

Funding

This work has been supported, in part, by a research grant from the University of Ferrara, (Fondo Ateneo Ricerca –FAR– 2020, Prof. Roberto Manfredini).

Authors' Contributions

Conceptualization, A.R. A.D.G., S.B., R.M.; Methodology, A.R., A.D.G., B.B.; Literary analysis, F.N., B.B., C.P.; Resources, A.R., R.M.; Writing – original draft preparation, A.R., A.D.G., S.B.; Writing – review and editing, F.N., B.B., C.P.; Supervision, R.M.; Project administration, A.R., A.D.G.; Funding acquisition, R.M. All authors have read and agreed to the published version of the manuscript.

ORCID ID

Alfredo De Giorgi: 0000-0002-0903-7825
Roberto Manfredini: 0000-0002-8364-2601

References

1) Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD; ESC Scientific Document Group. Fourth universal definition of myocardial infarction (2018). Eur Heart J 2019; 40: 237-269.
2) Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimský P, ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018; 39: 119-177.
3) Khera S, Kolte D, Gupta T, Subramanian KS, Khanna N, Aronow WS, Ahn C, Timmermans RJ, Cooper HA, Fonarow GC, Frishman WH, Panza JA, Bhatt DL. Temporal trends and sex differences in revascularization and outcomes of ST-segment elevation myocardial infarction in younger adults in the United States. J Am Coll Cardiol 2015; 66:1961-1972.
4) Kristensen SD, Laut KG, Fajadet J, Kaifoszova Z, Kala P, Di Mario C, Wijns W, Clemmensen P, Agladze V, Antoniades L, Alhabib KF, De Boer MJ, Claeys MJ, Deleanu D, Dudek D, Erglis A, Gilard M, Goktekin O, Guagliumi G, Gudnason T, Hansen KW, Huber K, James S, Janota T, Jennings S, Kajander O, Kanakakis J, Karamfiloff KK, Kedev S, Kornowski R, Ludman PF, Merkely B, Milicic D, Najafov R, Nicolini FA, Noc M, Ostojic M, Pereira H, Radovanovic D, Sabate M, Sobhy M, Sokolov M, Studencan M, Terzic I, Wahler S, Widimsky P. European Association for Percutaneous Cardiovascular Interventions. Reperfusion therapy for ST elevation acute myocardial infarction 2010/2011: current status in 37 ESC countries. Eur Heart J 2014; 35: 1957-1970.
5) Firman D, Arilaksono DG, Ambari AM, Radi B, Indriani S, Siagian SN, Pranata R, Alkatiri AA, Iryuza N, Mangkuanom AS. The obesity paradox: effect of body mass index on 2-years clinical out-

come after primary percutaneous coronary intervention in Indonesia. Eur Rev Med Pharmacol Sci 2021; 25: 4973-4982.

6) Ma Z, Ning B, Wu D, Liu WG, Guo YJ. Correlation between culprit vessel/tirofiban and reperfusion bradyarrhythmia in patients with ST-segment elevation myocardial infarction after emergency PCI. Eur Rev Med Pharmacol Sci 2021; 25: 5137-5144.

7) Gallerani M, Trappella G, Manfredini R, Pasin M, Napolitano M, Migliore A. Acute intracerebral haemorrhage: circadian and circannual patterns of onset. Acta Neurol Scand 1994; 89: 280-286.

8) Gallerani M, Portaluppi F, Maida G, Chieregato A, Calzolari F, Trapella G, Manfredini R. Circadian and circannual rhythmicity in the occurrence of subarachnoid hemorrhage. Stroke 1996; 27: 1793-1797.

9) Manfredini R, Boari B, Smolensky MH, Salmi R, la Cecilia O, Malagoni AM, Haus E, Manfredini F. Circadian variation in stroke onset: identical temporal pattern in ischemic and hemorrhagic events. Chronobiol Int 2005; 22: 417-453.

10) Manfredini R, Portaluppi F, Zamboni P, Salmi R, Gallerani M. Circadian variation in spontaneous rupture of abdominal aorta. Lancet 1999; 353: 643-644.

11) Manfredini R, Portaluppi F, Salmi R, Zamboni P, la Cecilia O, Kuwornu Afi H, Regoli F, Bigoni M, Gallerani M. Seasonal variation in the occurrence of nontraumatic rupture of thoracic aorta. Am J Emerg Med 1999; 17: 672-674.

12) Manfredini R, Gallerani M, Boari B, Salmi R, Mehta RH. Seasonal variation in onset of pulmonary embolism is independent of patients' underlying risk comorbid conditions. Clin Appl Thromb Hemost 2004; 10: 39-43.

13) Gallerani M, Boari B, Smolensky MH, Salmi R, Fabbri D, Contato E, Manfredini R. Seasonal variation in occurrence of pulmonary embolism: analysis of the database of the Emilia-Romagna region, Italy. Chronobiol Int 2007; 24: 143-160.

14) Citro R, Previtali M, Bovelli D, Vriz O, Astarita C, Patella MM, Provenza G, Armentano C, Ciampi Q, Gregorio G, Piepoli M, Bossone E, Manfredini R. Chronobiological patterns of onset of tako-tsubo cardiomyopathy: a multicenter Italian study. J Am Coll Cardiol 2009; 54: 180-181.

15) Muller JE, Stone PH, Turi ZG, Rutherford JD, Czeisler CA, Parker C, Poole WK, Passamani E, Roberts R, Robertson T, Sobel BE, Willerson JT, Braunwald E., and the MILIS Study Group. Circadian variation in the frequency of onset of acute myocardial infarction. N Engl J Med 1985; 313: 1315-1322

16) Cohen MC, Rohtla KM, Lavery CE, Muller JE, Mittleman MA. Meta-analysis of the morning excess of acute myocardial infarction and sudden cardiac death. Am J Cardiol 1997; 79: 1512-1516.

17) Manfredini R, Boari B, Bressan S, Gallerani M, Salmi R, Portaluppi F, Mehta RH. Influence of circadian rhythm on mortality after myocardial infarction: data from a prospective cohort of emergency calls. Am J Emerg Med 2004; 22: 555-559.

18) Manfredini R, Boari B, Salmi R, Fabbian F, Pala M, Tiseo R, Portaluppi F. Twenty-four-hour patterns in occurrence and pathophysiology of acute cardiovascular events and ischemic heart disease. Chronobiol Int 2013; 30: 6-16.

19) Manfredini R, Gallerani M, Portaluppi F, Fersini C. Relationships of the circadian rhythms of thrombotic, ischemic, hemorrhagic, and arrhythmic events to blood pressure rhythms. Ann N Y Acad Sci 1996; 783: 141-158.

20) Ornato JP, Peberdy MA, Chandra NC, Bush DE. Seasonal pattern of acute myocardial infarction in the National Registry of Myocardial Infarction. J Am Coll Cardiol 1996; 28: 1684-1688.

21) Manfredini R, Boari B, Smolensky MH, Salmi R, Gallerani M, Guerzoni F, Guerra V, Malagoni AM, Manfredini F. Seasonal variation in onset of myocardial infarction--a 7-year single-center study in Italy. Chronobiol Int 2005; 22: 1121-1135.

22) Manfredini R, Manfredini F, Boari B, Bergami E, Mari E, Gamberini S, Salmi R, Gallerani M. Seasonal and weekly patterns of hospital admissions for nonfatal and fatal myocardial infarction. Am J Emerg Med 2009; 27: 1097-1103.

23) Manfredini R, Fabbian F, De Giorgi A, Zucchi B, Cappadona R, Signani F, Katsiki N, Mikhailidis DP. Daylight saving time and myocardial infarction: should we be worried? A review of the evidence. Eur Rev Med Pharmacol Sci 2018; 22: 750-755.

24) Manfredini R, Fabbian F, Cappadona R, De Giorgi A, Bravi F, Carradori T, Flacco ME, Manzoli L. Daylight Saving Time and acute myocardial infarction: A meta-analysis. J Clin Med 2019; 8: 404.

25) Sipila JO, Ruuskanen JO, Rautava P, Kyto V. Changes in ischemic stroke following daylight saving time transitions. Sleep Med 2016; 27-28: 20-24.

26) Manfredini R, Casetta I, Paolino E, la Cecilia O, Boari B, Fallica E, Granieri E. Monday preference in onset of ischemic stroke. Am J Med 2001; 111: 401-403.

27) Manfredini R, Citro R, Previtali M, Vriz O, Ciampi Q, Pascotto M, Tagliamonte E, Provenza G, Manfredini F, Bossone E; Takotsubo Italian Network investigators. Monday preference in onset of takotsubo cardiomyopathy. Am J Emerg Med 2010; 28: 715-719.

28) Klastorin TD. An alternative method for hospital partition determination using hierarchical cluster analysis. Oper Res 1982; 30: 1134-1147.

29) Corrao S, Santalucia P, Argano C, Djade CD, Barone E, Tettamanti M, Pasina L, Franchi C, Kamal Eldin T, Marengoni A, Salerno F, Marcucci M, Kannucci PM, Nobili A, REPOSI Investigators. Gender-differences in disease distribution and outcome in hospitalized elderly: data from the REPOSI study. Eur J Intern Med 2014; 25: 617-623.

30) Mehta LS, Beckie TM, DeVon HA, Grines CL, Krumholz HM, Johnson MN, Lindley KJ, Vac-

carino V, Wang TY, Watson KE, Wenger NK; American Heart Association Cardiovascular Disease in Women and Special Populations Committee of the Council on Clinical Cardiology, Council on Epidemiology and Prevention, Council on Cardiovascular and Stroke Nursing, and Council on Quality of Care and Outcomes Research. Acute Myocardial Infarction in Women: A Scientific Statement From the American Heart Association. Circulation 2016; 133: 916-947.

31) Dakota I, Munawar M, Pranata R, Raffaello WM, Sukmawan R. Diagnostic prediction model in subjects with low-risk unstable angina pectoris/non-ST segment Elevation Myocardial Infarction. Eur Rev Med Pharmacol Sci 2021; 25: 5145-5152.

32) Young S, Linden W, Ignaszewski A, Con A, Terhaag S, Campbell T. Psychosocial and medical predictors of 1-year functional outcome in male and female coronary bypass recipients. Heart Mind 2019; 3: 113-121.

33) Emami AS, Merz CN, Eastwood JA, Pepine CJ, Handberg EM, Bittner V, Mehta PK, Krantz DS, Vaccarino V, Eteiba W, Cornell CE, Rutledge T. Somatic versus cognitive depressive symptoms as predictors of coronary artery disease among women with suspected ischemia: The women's ischemia syndrome evaluation. Heart Mind 2021; 5: 112-118.

34) Henriques JP, Haasdijk AP, Zijlstra F; Zwolle Myocardial Infarction Study Group. Outcome of primary angioplasty for acute myocardial infarction during routine duty hours versus during off-hours. J Am Coll Cardiol 2003; 41: 2138-2142.

35) De Luca G, Suryapranata H, Ottervanger JP, van't Hof AW, Hoorntje JC, Gosselink AT, Dambrink JH, Zijlstra F, de Boer MJ. Circadian variation in myocardial perfusion and mortality in patients with ST-segment elevation myocardial infarction treated by primary angioplasty. Am Heart J 2005; 150: 1185-1189.

36) Glaser R, Naidu SS, Selzer F, Jacobs AK, Laskey WK, Srinivas VS, Slater JN, Wilensky RL. Factors associated with poorer prognosis for patients undergoing primary percutaneous coronary intervention during off-hours: biology or systems failure? JACC Cardiovasc Interv 2008; 1: 681-688.

37) Ofoma UR, Basnet S, Berger A, Kiechner HL, Girotra S, for the American Heart Association Get With the Guidelines – Resuscitation Investigators. Trends in survival after in-hospital cardiac arrest during night and weekends. J Am Coll Cardiol 2018; 71: 402-411.

38) Manfredini R, De Giorgio R, Fabbian F. Off-hours and in-hospital mortality: lower resources or higher severity? J Am Coll Cardiol 2018; 71: 2492.

39) LaBounty T, Eagle KA, Manfredini R, Fang J, Tsai T, Smith D, Rubenfire M. The impact of time and day on the presentation of acute coronary syndromes. Clin Cardiol 2006; 29: 542-546.

40) Cortegiani A, Ippolito M, Misseri G, Helviz Y, Ingoglia G, Bonanno G, Giarratano A, Rochwerg B, Einay S. Association between night/after-hours surgery and mortality: a systematic review and meta-analysis. Br J Anaesth 2020; 124: 623-637

41) Wang L, Gan X, Wang X, Wang K, Yan H, Wang Z, Chen L. Does time of day influences outcome in out-of-hospital cardiac arrest patients? A meta-analysis of cohort studies. Medicine (Baltimore) 2020; 99: e22290.

42) Yu YY, Zhao BW, Ma L, Dai XC. Association between out-of-hour admission and short- and long-term mortality in acute myocardial infarction: a systematic review and meta-analysis. Front Cardiovasc Med 2021; 8: 752675.

43) Manfredini R, La Cecilia O, Boari B, Steliu J, Michelini V, Carli P, Zanotti C, Bigoni M, Gallerani M. Circadian pattern of emergency calls: implications for ED organization. Am J Emerg Med 2002; 20: 282-286.

44) Peng H, Sun Z, Di B, Ding X, Chen H, Li H. Contemporary impact of circadian symptom-onset patterns of acute ST-Segment elevation myocardial infarction on long-term outcomes after primary percutaneous coronary intervention. Ann Med 2021; 53: 247-256.

45) Manfredini R, Salmi R, Cappadona R, Signani F, Basili S, Katsiki N. Sex and circadian periodicity of cardiovascular diseases. Are women sufficiently represented in chronobiological studies? Heart Fail Clin 2017; 13: 719-738.

46) Leibowitz D, Planer D, Weiss T, Rott D. Seasonal variation in myocardial infarction is limited to patients with ST-elevations on admission. Chronobiol Int 2007; 24: 1241-1247.

47) Manfredini R, Fabbian F, Pala M, Tiseo R, De Giorgi A, Manfredini F, Malagoni AM, Signani F, Andreati C, Boari B, Salmi R, Imberti D, Gallerani M. Seasonal and weekly patterns of occurrence of acute cardiovascular diseases: does a gender difference exist? J Womens Health (Larchmt) 2011; 20: 1663-1668.

48) Chongprasertpon N, Coughlan JJ, Cahill C, Kiernan TJ. Circadian and seasonal variations in patients with acute STEMI: A retrospective. single PPCI center study. Chronobiol Int 2018; 35: 1663-1669.

49) Mahajan AM, Gandhi H, Smilowitz NR, Roe MT, Hellkamp AS, Chiswell K, Gulati M, Reynolds HR. Seasonal and circadian patterns of myocardial infarction by coronary artery disease status and sex in the ACTION Registry-GWTG. Int J Cardiol 2019; 274: 16-20.

50) Keller K, Hobohm L, Münzel T, Ostad MA. Sex-specific differences regarding seasonal variations of incidence and mortality in patients with myocardial infarction in Germany. Int J Cardiol 2019; 287: 132-138.

51) Vallabhajosyula S, Patlolla SH, Cheungpasitporn W, Holmes DR, Gersh BJ. Influence of seasons on the management and outcomes acute myocardial infarction: An 18-year US study. Clin Cardiol 2020; 43: 1175-1185.

52) Hodzic E, Perla S, Iglica A, Vucijak M. Seasonal incidence of acute coronary syndrome and its features. Mater Sociomed 2018; 30: 10-14.

53) Kloner RA, Das S, Poole WK, Perrit R, Muller J, Cannon CP, Braunwald E. Seasonal variation of myocardial infarct size. Am J Cardiol 2001; 88: 1021-1024.

54) Panagiotakos DB, Chrysohoou C, Pitsavos C, Nastos P, Anadiotis A, Tentolouris C, Stefanadis C, Toutouzas P, Paliatsos A. Climatological variations in daily hospital admissions for acute coronary syndromes. Int J Cardiol 2004; 94: 229-233

55) Lee JH, Chae SC, Yang DH, Park HS, Cho Y, Jun JE, Park WH, Kam S, Lee WK, Kim YJ, Kim KS, Hur SH, Jeong MH; Korea Acute Myocardial Infarction Registry Investigators. Influence of weather on daily hospital admissions for acute myocardial infarction (from the Korea Acute Myocardial Infarction Registry). Int J Cardiol 2010; 144: 16-21.

56) Nagarajan V, Fonarow GC, Ju C, Pencina M, Laskey WK, Maddox TM, Hernandez A, Bhatt DL. Seasonal and circadian variations of acute myocardial infarction: findings from the Get With The Guidelines-Coronary Artery Disease (GWTG-CAD) program. Am Heart J 2017; 189: 85-93.

57) Mehta RH, Manfredini R, Bossone E, Fattori R, Evagelista A, Boari B, Cooper JV, Sechtem U, Isselbacher EM, Nienaber CA, Eagle KA; International Registry of Acute Aortic Dissection (IRAD) Investigators. The winter peak in the occurrence of acute aortic dissection is independent of climate. Chronobiol Int 2005; 22: 723-729.

58) Gallerani M, Boari B, Manfredini F, Manfredini R. Seasonal variation in heart failure hospitalization. Clin Cardiol 2011; 34: 389-394.

59) Gebhard C, Gebhard CE, Stähli BE, Maafi F, Bertrand MJ, Wildi K, Fortier A, Onandia ZG, Toma A, Zhang ZW, Smith DC, Spagnoli V, Ly HQ. Weather and risk of ST-elevation myocardial infarction revisited: Impact on young women. PLoS One 2018; 13: e0195602.

60) Alnsasra H, Zahger D, Geva D, Matetzky S, Beigel R, Iakobishvili Z, Alcalai R, Atar S, Shimony A. Contemporary determinants of delayed benchmark timelines in acute myocardial infarction in men and women. Am J Cardiol 2017; 120: 1715-1719.

61) Jackson J, Alkhalil M, Ratcovich H, Wilkinson C, Mehran R, Kunadian V. Evidence base for the management of women with non-ST elevation acute coronary syndrome. Heart 2022; 108: 1682-1689.

62) Murphy AC, Yudi MB, Farouque O, Dinh D, Duffy SJ, Brennan A, Reid CM, Andrianopoulos N, Koshy AN, Martin L, Dagan M, Freeman M, Blusztein D, Ajani AE, Clark DJ; Melbourne Interventional Group. Impact of gender and door-to-balloon times on long-term mortality in patients presenting with ST-Elevation Myocardial Infarction. Am J Cardiol 2019; 124: 833-841.

63) Ladwig KH, Meisinger C, Hymer H, Wolf K, Heier M, von Scheidt W, Kuch B. Sex and age specific time patterns and long term time trends of pre-hospital delay of patients presenting with acute ST-segment elevation myocardial infarction. Int J Cardiol 2011; 152: 350-355.

64) Benamer H, Bataille S, Tafflet M, Jabre P, Dupas F, Laborne FX, Lapostolle F, Lefort H, Juliard JM, Letarnec JY, Lamhaut L, Lebail G, Boche T, Loyeau A, Caussin C, Mapouata M, Karam N, Jouven X, Spaulding C, Lambert Y. Longer pre-hospital delays and higher mortality in women with STEMI: the e-MUST Registry. EuroIntervention 2016; 12: e542-549.

65) Poorhosseini H, Saadat M, Salarifar M, Mortazavi SH, Geraiely B. Pre-Hospital delay and its contributing factors in patients with ST-elevation myocardial infarction: a cross sectional study. Arch Acad Emerg Med 2019; 7: e29.

66) ALAhmadi AF, ALSaedi MF, Alahmadi AE, Alharbi MG, Alharbi IH, Radman Al-Dubai SA. Pre-hospital delay among patients with acute myocardial infarction in Saudi Arabia. A cross-sectional study. Saudi Med J 2020; 41: 819-827.

67) Lee SH, Kim HK, Jeong MH, Lee JM, Gwon HC, Chae SC, Seong IW, Park JS, Chae JK, Hur SH, Cha KS, Kim HS, Seung KB, Rha SW, Ahn TH, Kim CJ, Hwang JY, Choi DJ, Yoon J, Joo SJ, Hwang KK, Kim DI, Oh SK; KAMIR Investigators. Pre-hospital delay and emergency medical services in acute myocardial infarction. Korean J Intern Med 2020; 35: 119-132.

68) Shah T, Haimi I, Yang Y, Gaston S, Taoutel R, Mehta S, Lee HJ, Zambahari R, Baumbach A, Henry TD, Grines CL, Lansky A, Tirziu D. Meta-analysis of gender disparities in in-hospital care and outcomes in patients with ST-segment elevation myocardial infarction. Am J Cardiol 2021; 147: 23-32.