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

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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 procedures 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 ischemia1. 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 erosion1. 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 disease2. 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 worldwide2. STEMI affects generally younger people and is more common in men than in women2, and mortality is influenced by many factors, such as advanced age, Killip class, time delay to treatment, presence of emergency
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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). Interestingly, some studies 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. Timely corresponding treatments and reduction of reperfusion damage are of great significance for STEMI patients. 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 from our group. As for AMI, after the first milestone study by Muller et al., many studies 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. 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, and variations in sympathetic tone, catecholamine secretion, and blood pressure are also implicated. Moreover, a series of studies 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. 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.

The aim of the present study was to investigate the chronobiological patterns and possible sex-specific differences in a single-center cohort of type I 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. 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. 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 χ², 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, 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).
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 ($p=0.00081$, $p=0.05$, $p=0.0141$, 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.

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% C.I.</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>1.879</td>
<td>1.185 - 2.978</td>
<td>0.007</td>
</tr>
<tr>
<td>Age</td>
<td>1.051</td>
<td>1.029 - 1.073</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Personal history of cardiovascular disease</td>
<td>1.880</td>
<td>1.064 - 3.321</td>
<td>0.030</td>
</tr>
</tbody>
</table>

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

Although women live longer than men\textsuperscript{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\textsuperscript{30}. In fact, sex-specific differences exist in the presentation, pathophysiological mechanisms, and outcomes in patients with AMI\textsuperscript{30}. For example, sex/gender (and age) have a value of diagnostic validity in the prediction models of unstable angina pectoris and NSTEMI\textsuperscript{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\textsuperscript{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\textsuperscript{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
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 Again, Ofoma et al.\(^3\) 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.\(^3\)4 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). 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 \( (p=0.033) \). Very recently, a series of systematic reviews\(^4\) and meta-analyses provided robust confirmation on this topic. Cortegiani et al.\(^9\) (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.\(^1\) (10 cohort studies, more than 250,000 cases), found that nighttime 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.\(^2\) (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 \( (OR: 1.04 \text{ and } 1.03, \text{ respectively}) \).

**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,
and acute poisoning. 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. 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 chronobiological studies dealing with life-threatening acute cardiovascular diseases, observed that 44% of studies 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. 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.

**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 have shown a winter preference for AMI onset others gave negative results. 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. 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

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

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

**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, CAGB 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. 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). The “cold stress” could increase the severity of an event rather than trigger its development. 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. 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. 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. Older patients with myocardial infarction have a reduced physiological reserve during winter, following a higher incidence of pulmonary inflammatory events due to low temperatures, 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. 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.

### 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. Alnasr et al. 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. 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 mediatric 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, P2Y12 inhibitors, statins) and revascularization treatments (angiography, PCI). Moreover, sex-specific differences are evident for clinical outcomes as well. An Australian study 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. The reasons are unknown, although it is possible that females could frequently suffer from atypical symptoms during the acute phase of AMI. 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. confirmed that females had significantly longer delays to first medical contact (mean difference 4.25 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 (worse 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.

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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.

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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.

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References

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-


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38) 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.


