ASSOCIATION OF SEX AND AGE AND DELAY PREDICTORS ON THE TIME OF PRIMARY ANGIOPLASTY ACTIVATION FOR MYOCARDIAL INFARCTION PATIENTS IN AN EMERGENCY DEPARTMENT

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

ETHICAL STATEMENT

The study was approved by the Clinical Research Ethics Committee of the hospital (IIBSP-IAM-2015-84, IIBSP-IAM-2015-84v2) and conducted in accordance with the Declaration of Helsinki.

FUNDING

The Government of Catalonia (Spain) provided funding for this research, with a grant issued in 2019 within the framework of the Strategic Health Research and Innovation Plan (PERIS) 2016-2020 to Gemma Berga Congost, with the file code SLT008/18/00052.

ROLE OF THE FUNDING SOURCE

The funders of the study played no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

CLINICAL TRIALS REGISTRY

Registration number: NCT04333381

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MANUSCRIPT DETAILS

Words: 3645 manuscript and 246 abstract

Tables: 4; Figures: 3

ICMJE DISCLOSURE FORM

Date: 3/12/2022

Your Name: Gemma Berga Congost

Manuscript Title: ASSOCIATION OF GENDER AND AGE ON THE TIME OF PRIMARY ANGIOPLASTY ACTIVATION FOR MYOCARDIAL INFARCTION PATIENTS AT EMERGENCY DEPARTMENT

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Your Name: Maria Antonia Martinez Momblan

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Your Name: Judit Ruiz Gabalda

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Your Name: Jonatan Valverde Bernal

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Date: 3/12/2022

Your Name: Mireia Puig Campmany

Manuscript Title: ASSOCIATION OF GENDER AND AGE ON THE TIME OF PRIMARY ANGIOPLASTY ACTIVATION FOR MYOCARDIAL INFARCTION PATIENTS AT EMERGENCY DEPARTMENT

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Date: 3/12/2022

Your Name: Adrian Marquez Lopez

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Date: 3/12/2022

Your Name: Salvatore Brugaletta

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HIGHLIGHTS

- Time delays in STEMI patients admitted to Emergency Department (ED) are longer in women and elderly
- STEMI delays are longer particularly in women and elderly with atypical presentation
- Older and first medical contact outside the ED have longer activation time
- Gender and age are not associated with a longer activation time in young people
- Activation time is particularly longer in older women

Authors' Point-by-Point Response to the reviewers' Reports

Manuscript Number: HL-D-22-00168

Title:

ASSOCIATION OF SEX AND AGE AND DELAY PREDICTORS ON THE TIME OF PRIMARY ANGIOPLASTY ACTIVATION FOR MYOCARDIAL INFARCTION PATIENTS IN AN EMERGENCY DEPARTMENT

Point-by-point response to editors and reviewers

Firstly, we would like to thank to the editors and reviewers of Heart & Lung for reviewing our manuscript and making the comments needed to improve the text. We have made point by point corrections for each comment. The authors have tried to address all the issues raised by the reviewers.

Point-by-point response to reviewers

EDITOR IN CHIEF

Question: Thank you for your responsiveness to the previous review. Important predictors of health care outcomes in many areas are socioeconomic status, race, and ethnicity. If you have data available it would be helpful to include. If not, this may be a limitation. Please discuss. Thanks.

Response: Thank you for your comment.

Unfortunately, we did not collect socioeconomic status and we included now the following sentence in limitations: Data about socioeconomic status were not collected (Page 18 line 1 to 2)

Regarding race and ethnicity over 98% of the study population was Caucasian/European. Therefore, the conclusions of the present study should be limited to this ethnical group.

The following sentence has been added to the limitations section: Over 98% of the study population was Caucasian/European. Therefore, the conclusions of the present study should be limited to this ethnical group. (Page 18 line 3 to 4)

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ABSTRACT

Background: Time between Emergency Department (ED) and ST-segment elevation acute myocardial infarction (STEMI) activation time is a good indicator of ED quality. STEMI delays are of particular importance in some subgroups, such as women and the elderly.

Objective: To determine the association of sex and age with activation time in STEMI patients admitted to the ED.

Methods: An observational retrospective study was conducted including all patients admitted to the ED activated as a STEMI. The main variable was activation time. To evaluate the independent predictors of activation time, a multivariate logistic regression analysis was carried out, variables were sex, age, sex and age combined, chest pain, ST elevation in the electrocardiogram, and first medical contact (FMC) at the hospital's ED.

Results: A total of 330 patients were included. They were classified by sex: 23.9% (78) women and 76.1% (249) men; and age: 51.1% (167) <65 yo and 48.9% (160) ≥65 yo. Women and elderly patients exhibited a more atypical presentation. Multivariate analysis shows that showed that elderly age (OR=1.976 95%; CI=1.257-3.104; **p=0.003**) and FMC prior to attending the ED (OR=1.762; 95% CI=1.117-2.779; **p=0.015**) were associated with a longer activation time. Women older than 65 years old showed the longest activation time.

Conclusion: STEMI delays are longer in women and the elderly with atypical presentation. Age ≥65 and FMC outside the ED were associated with an increase in the activation time. This highlights the need to develop strategies to improve activation time for these specific patient groups.

Keywords: Sex, Age, STEMI, Emergency Department, Acute Coronary Syndrome, Myocardial infarction

ABBREVIATIONS LIST

CAD: Coronary Artery Disease

CRA: Cardiorespiratory Arrest

DLP: Dyslipidaemia.

DM: Diabetes Mellitus.

ECG: Electrocardiogram

ED: Emergency Department

ESC: European Society Of Cardiology

FMC: First Medical Contact

GPC: General Poor Condition.

HTA: Arterial Hypertension

IC: Interventional Cardiology

Min: Minutes

PCI: Percutaneous Coronary Intervention

STEMI: St-Segment Elevation Acute Myocardial Infarction

Yo: Years Old

INTRODUCTION

Early diagnosis and treatment of ST-segment elevation acute myocardial infarction (STEMI) are fundamental and time delays have a direct impact on subsequent mortality and morbidity.[1] Diagnosis and activation of primary percutaneous coronary intervention (PCI) for STEMI can be performed by out-of-hospital emergency services, primary care, hospitals without primary PCI capacity or directly by the Emergency Department (ED) of a hospital with primary PCI capacity. Patients attending a PCI centre had a lower Door-to-balloon time than those attending a non-PCI centre and, consequently, lower in-hospital mortality.[2]

Patients who go by themselves to the ED of a hospital with primary PCI capacity experience a longer delay than patients who contact the emergency medical services by directly calling the emergency number.[3]

The time between arrival at the ED and activation of primary PCI for STEMI is a good indicator of the quality of ED services. The STEMI clinical guidelines of the European Society of Cardiology (ESC) recommend an interval between first medical contact (FMC) and electrocardiogram (ECG) of less than 10 minutes (min), and an interval between diagnosis and balloon angioplasty of less than 60 min when the patient attends the ED of a hospital with primary PCI capacity.[4]

Also, there are several sociodemographic and clinical factors that increase the delay in STEMI treatment, such as sex (women), age (elderly), diabetes, non-smoking habit, previous cardiac history, atypical clinical and electrocardiographic presentation and unstable medical condition that requires stabilization.[5,6]

Furthermore, other research highlighted the persistence of a sex and age gap as regards STEMI diagnosis and treatment. Women receive later, inadequate treatment and their

mortality rate is higher.[7-12] Likewise, elderly patients are underdiagnosed and inadequately treated, resulting in a worse prognosis and survival rate.[13-15] For both groups, this delay is primarily attributed to the atypical signs and symptoms presented by women and elderly patients.[16–17]

There were previous records available that analysed the association of sex and age with STEMI delays and even the combination of both, but they did not specifically focus on the time between arrival at the ED and activation of primary PCI in STEMI patients admitted and diagnosed in the ED of a hospital with primary PCI capacity.[18,19] Moreover, it is unknown whether the two factors in combination multiply the delays in activation time.

The hypotheses were:

- Response times in STEMI patients who directly attend the ED of our hospital with primary PCI capacity are elevated.
- Women and the elderly who attend the ED of our hospital present a more atypical/infrequent clinical condition, which carries a greater diagnostic difficulty.
- Sex and age are predictors of delay in Activation time and time between FMC and STEMI activation.
- Given that sex and age increase delays in STEMI, jointly, both multiply the delay in Activation time.

The main objective of the study was to determine the association of sex and age with activation time in patients admitted to the ED of a hospital with primary PCI capacity and activated as a code STEMI.

The specific objectives were to identify the predictors of delay on the activation time and evaluate whether being a woman and older multiplied the ED–activation delay.

METHODS

Study design and setting

This was an observational retrospective study conducted at a hospital with primary PCI capacity between January 2013 and January 2017. The Interventional Cardiology (IC) Unit of the Hospital de la Santa Creu i Sant Pau (HSCSP) in Barcelona (Spain) provides STEMI cover to a population of 1,253,266 inhabitants, providing 24-hour cardiac catheterization facilities since 2006, and has formed part of the *Codi IAM* network of the Catalan Healthcare System since 2009. The study population was composed of consecutive patients who meet the inclusion and exclusion criteria, with suspected STEMI activated as code STEMI by the ED of our hospital. Inclusion criteria were: patients ≥18 years old, admitted to the ED of the hospital. All patients who had a first medical contact outside the ED without a clear STEMI diagnosis and were then admitted to the ED for a final diagnosis were also included. Exclusion criteria were: patients identified as STEMI in other hospitals without primary PCI capacity or in primary care centres and activated as code STEMI because these patients bypassed the ED. Patients who did not undergo coronary angiography and pregnant women were also excluded.

The total population of patients activated as a STEMI in the hospital within the study period was 1,687. Of these, 330 were patients activated from the ED of the hospital itself, meeting the inclusion/exclusion criteria. Three of these patients were excluded: two patients died before arriving at the interventional cardiology (IC) unit, and one had an alternative diagnosis immediately after being activated as code STEMI, which was immediately deactivated. This resulted in a final sample of 327 patients. In order to determine the association of sex and age with STEMI diagnosis and treatment times, the sample was divided into two groups: sex (male and female) and age (<65 and ≥65). The

age group was established based on the average age of the whole sample, which was 64±14. All variables were compared between these groups.

The study was approved by the Clinical Research Ethics Committee of the hospital (IIBSP-IAM-2015-84, IIBSP-IAM-2015-84v2) and conducted in accordance with the Declaration of Helsinki.

The primary outcome was sex and age-based differences in Activation time, that is the time between ED arrival and primary PCI activation, defined as the time to call the IC team (≤ 10 min was optimal).[2] Additionally, another outcome of interest included sex and age-based differences in FMC–Activation time, that is the time from FMC to time of the call to the IC team. The FMC was the initial contact with health professionals capable of obtaining and interpreting an ECG and performing the initial interventions outside the ED, but who had not been diagnosed and activated as a STEMI before arrival at the ED. An adequate FMC–Activation time was considered the same as the Activation time.

Other time variables were also collected and analysed. Pain time was defined as the time from the onset of symptoms and/or events. ECG time was defined as the time to perform and interpret the ECG. ED time was defined as the time from arrival at the ED of the hospital where the study was conducted and balloon time was defined as wiring of the culprit lesion. All time variables were measured in minutes. (**Figure 1) (Table2)**.

Main clinical variables and comorbidities, all-cause in-hospital mortality, hospital stay (in days, day 1 being the day of admission to the ED of our hospital until discharge), and false STEMI positives were also recorded. False positives were defined according to a) angiographic definition, which includes patients without a culprit coronary artery, and b) clinical definition, which includes patients with a discharge diagnosis other than STEMI.[20]

The criteria used to identify STEMI patients were the presence of symptoms or signs (ECG) indicating myocardial ischemia. Regarding the symptomatology, persistent oppressive chest pain with or without irradiation to the left arm, neck and jaw were considered typical and abdominal, scapular, back and nonspecific pain, dyspnea, fatigue, malaise, nausea/vomiting and syncope as atypical.[4]

As for the signs, a typical electrocardiogram was defined, as per current guidelines, as ST elevation in two contiguous leads (> 2 mm for men and 1.5-1 mm for women) and atypical as an ECG with no clear ST-segment elevation considered apt for PCI in patients with ongoing symptoms consistent with myocardial ischemia. Therefore, patients with the following electrocardiographic presentations were included: left bundle branch block, right bundle branch block, ventricular paced rhythm, isolated posterior myocardial infarction, ischemia due to left main coronary artery occlusion or multivessel disease with ST depression ≥1 mm in eight or more surface leads coupled with ST-segment elevation in a VR and/or V1 and hyperacute T waves, which may precede ST segment elevation.[4]

Data collection

All clinical variables were gathered retrospectively using the Data Collection Register, based on the recommendations of the ESC clinical guidelines.[2] The symptoms were included based on the clinical records drafted by the ED doctor, cardiologist, ED and IC nurses. The time variables were recorded prospectively by the IC on-call team and transferred to the registry network of the Catalan Healthcare System (*Codi IAM*), which is regularly audited. Moreover, all the data was collected from the information terminal of the code STEMI registry, a database containing all the clinical variables and response times belonging to the *Codi IAM* Catalan Emergency STEMI Care network.

Statistical analysis

We calculated the sample size by considering the activation time. Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a one-sided test, 22 subjects were necessary in the male group and 74 in the female group to discriminate a difference ≥ 6 minutes as statistically significant. The common standard deviation was assumed to be 9.43. A drop-out rate of 10% was anticipated. This determination was made based on the results of Dreyer RP *et al.*[18] The calculation was performed with the Granmo sample size calculator v.7.21.

The sampling technique was non-probabilistic and consecutive. A descriptive analysis was conducted, using absolute number and percentage for categorical variables, as well as mean value with standard deviation for quantitative variables with a normal distribution, and median with interquartile range for quantitative variables with a non-normal distribution. Categorical variables were compared using the Chi-squared test or Fisher's exact test, as applicable, while the quantitative variables were compared with the ANOVA or Mann-Whitney U test, depending on their distribution.

To evaluate the independent predictors of activation time, a multivariate logistic regression analysis was carried out, with all variables with $p<0.10$ in the univariate analysis being entered in order to minimize any confounding factors. To evaluate the independent predictors of the activation time, a multivariate logistic regression analysis was carried out, with all variables with $p<0.10$ in the univariate analysis being entered in order to minimize any confounding factors. The variables taken into consideration were sex, age (<65 and ≥65 years), sex and age combined, smoking, chest pain at presentation, elevation of the ST-segment in the ECG, and FMC at the ED of the hospital under study. Moreover, a multivariate logistic regression analysis was conducted to evaluate the predictors of FMC and activation time. The variables taken

into consideration were the patient's sex, age (<65 and ≥65 years), sex and age combined, smoking, chest pain at presentation, ST-segment elevation in the ECG, and FMC at the ED of the hospital under study.

To validate the logistic regression model with the dependent variable Activation time, the statistical method of Hosmer and Lemeshow revealed a value of p=0.991. Additionally, the AUC value was calculated, with a result of 0.605 (p=0.001). For the FCM-Activation time variable, the Hosmer and Lemeshow test revealed a value of p=0.998 and the AUC value was 0.752 ($p < 0.001$).

A 2-tailed level of significance of 5% ($\alpha=0.05$) was used. All analyses were conducted using the IBM–SPSS (V22.0) statistical package.

RESULTS

Study population

The final sample was 327 patients. In 75.23% (n=246) of cases, a primary PCI was carried out and 12.8% (n=42) of the STEMIs activated were false positives. The sample was divided into groups by sex, 23.9% women (n=78) and 76.1 men % (n=249), and also age, with 51.1% (n=167) in the <65 group, and 48.9% (n=160) in the ≥65 group (**Figure 2**).

Women who suffered a STEMI tended to be older than the men and more often presented atypical symptoms. **(Table 1)**.

Elderly patients had a great number of cardiovascular risk factors and comorbidities, compared with younger patients, with atypical symptoms, and presented a more serious condition on arrival at the hospital, with a more advanced Killip Class. **(Table 1)**.

In-hospital all-cause mortality was 11.6% (n=38). A multivariate analysis of the clinical factors related to in-hospital mortality was performed obtaining significant results for arterial hypertension, (OR=3.102; 95% CI=1.111–8.662; p=0.031) smoking, (OR=3.828; 95% CI=1.484–9.877; p=0.006) and Killip IV (OR=11.289; 95% CI=2.97–42.901; p<0.001).

Outcome data (Table 2)

The activation and the FMC–Activation times were longer in elderly vs. younger patients. On the contrary, FMC–activation was longer in women vs. men, but activation time did not show any differences according to sex. The longest time was detected in women > 65 years old. **(Figure 3)**.

When considering the activation time, the univariate analysis showed that age > 65 yo (**p=0.010**) and FMC outside the ED (**p=0.049**) were associated with the longer time; at

the multivariate analysis, age > 65 yo (OR=1.976; 95% CI=1.257- 3.104; **p=0.003**) and FMC outside the ED (OR=1.762; 95% CI=1.117-2.779; **p=0.015**) were independent predictors of a longer activation time. **(Table 3)**.

When considering the FMC–activation time, the univariate analysis showed that sex (female) (**p=0.026**), age (>65 yo) (**p=0.007**), sex and age interaction (**p=0.006**), atypical chest pain (**p<0.001**), atypical electrocardiogram (**p<0.001**) and FMC outside the ED (**p<0.001**) were associated with a longer delay time. However, in the multivariate analysis, only atypical chest pain (OR=2.547; 95% CI=1.343-4.831; **p=0.004**), atypical electrocardiogram (OR=3.036; 95% CI=1.542-5.979; **p=0.001**) and FMC outside the ED (OR=4.747; 95% CI=2.875-7.838; **p<0.001**) were independent predictors of a longer FMC–activation time. **(Table 4)**.

DISCUSSION

This study shows that the activation time of primary PCI for STEMI patients is longer in elderly vs. younger patients; however, it does not differ between men and women. When considering the time between FMC and activation of primary PCI, this was longer both in the elderly and women compared with younger and male patients. The study also showed that the predictors of delay in the activation time were age ≥65 and an FMC outside the hospital which did not result in STEMI identification until arriving at the ED. Lastly, there was no positive association between sex and age among patients under 65 years old, however, in patients over 65, women were observed to present a longer activation time than men.

Our results confirm other previous reports, that women and elderly patients more frequently present atypical symptoms or, in other words, less commonly present chest pain than men or patients under 65 years.[21-23] As a consequence, there was a greater delay in STEMI response times.[24,25] Therefore, to facilitate early diagnosis in the case of women and elderly patients, other atypical symptoms should be considered, such as abdominal, scapular and rib pain or general malaise/tiredness in women; and abdominal and rib pain, dyspnoea, syncope and general malaise/tiredness among elderly patients.[17,21-23] Most studies base their conclusions on the typical STEMI profile (men under 65 years old) and little attention has been focused on STEMI from the perspective of sex and age. For this reason, the most widely studied clinical profile is young men who usually present with chest pain. Various studies showed that the clinical presentation of STEMI may be different in women and elderly patients.[21-23]

In addition, some authors question the terms “typical” and “atypical” as evaluation standards, emphasizing the need for the differences to be established according to the symptomatic profiles of women and men, highlighting the need to standardize the

evaluation of symptoms but not the experience of these symptoms.[23,26,27] It is therefore essential to ensure that the sex and age perspective is included in research so that the signs and symptoms of STEMI are suitably defined.

Compared with other previous registries that analysed delays in PCI vs non-PCI centres, it was confirmed that patients attending a PCI centre had a lower Door-to-balloon time than those attending a non-PCI centre. However, in our registry, door-to-balloon time showed higher delays than in other PCI centres and higher in-hospital mortality was also observed, which could be justified as it included those who presented out-of-hospital cardiac arrest in the study population.[28]

Other authors also studied the association between sex and age related to mortality in STEMI and concluded that young women had a higher mortality, however, in our record we only observed that arterial hypertension, smoking and Killip IV were predictors of all-cause in-hospital mortality in STEMI.[29,30]

The study confirms that all STEMI diagnosis and treatment times were longer in the case of women and particularly among elderly patients, thus thorough vigilance is required in such cases.[12,14,16,25,30,31] In contrast with other studies, the primary outcome was the Activation Time of a hospital with primary PCI capacity,[18,19] because this is considered to be an indicator of optimal quality that demonstrates the ED's response capacity, thereby enabling subsequent continuous improvement strategies to be designed and implemented to enhance the healthcare quality of the hospital's ED.[32] On the other hand, although other studies compared STEMI management and outcomes between men and women, in our registry, we also established a comparison between elderly and younger patients and the association between both.[18]

Moreover, this study shows that advanced age is a predictor of a long activation time and confirms that women > 65 years present a greater delay in STEMI.[19]

This should be taken into account, especially in a pandemic situation such as COVID-19. Different registries have shown that the times for diagnosis and treatment of STEMI were higher during the pandemic,[33] which could imply a longer delay in these groups.

In contrast with other studies, when the FMC-activation data were analysed overall, neither sex nor age were seen to directly impact on the delay in this interval.[24] However, presenting atypical STEMI signs and symptoms and having a prior FMC before attending the ED were shown to be factors that increased this delay. This begs the question of whether the delay is really due to being a woman or elderly or to the atypical presentation that these groups of patients more often have.

Our study provides new data on the age and sex gap, revealing that there is no association between sex and age among young people but that, in the case of patients over 65 years old, there was a longer delay in the activation time for women.

Our registry highlights that the gap in the diagnosis and treatment of STEMI in women and the elderly persists. As suggested by other authors, bias presented by professionals associated with these groups of patients could cause the delay in FMC-balloon time.[34] It might be due to an underestimation of symptoms in these groups by ED professionals, especially when they present a more atypical or infrequent clinical picture. An automated "physician-blind" STEMI activation system, which eliminates the bias of professionals in women and the elderly, is associated with a reduction in treatment delays,[34] but it would be complex to implement in our environment and population since they are patients who come in person to the ED. Specific updating and continuous training regarding the clinical condition of women and the elderly could be a useful and feasible tool to improve the early diagnosis of STEMI in these groups and reduce the Activation time. Future research should be conducted to demonstrate the impact on activation time of education for nurses and emergency physicians in those more atypical or infrequent STEMI presentations.

And finally, as recommended by the ESC clinical guidelines, in order to ensure continuous improvement in the treatment of STEMI, regular audits must be conducted at an individual (hospital) and collective level (STEMI healthcare network), with studies being designed to enable quality of care and clinical outcomes to be monitored according to sex and age, to improve these parameters and eliminate the differences that exist in our setting.

LIMITATIONS

Retrospective data collection presents limitations due to its single-hospital and retrospective design, thus the results for Activation time and FMC-Activation time delays can only generate hypotheses for the factors that could contribute to reducing STEMI response times. In this study, this issue was minimized because standardised records were available and implemented throughout the entire National Healthcare System. The registration form used was specifically for the Catalan Public Healthcare System, however, many of the items contained are common to the forms used by other national and international registries and, therefore, their results were comparable. Another limitation could be that the data collected represents a picture of the population and Health Care System from between 2013 and 2017, which could be argued to be different nowadays. However, since 2013, there has not been an active consciousness campaign for ED healthcare workers in terms of clinical presentation and how to proceed in women and the elderly and, therefore, even if the global time delays might be better now, we do not believe there has been any change in these special groups.

And finally, although a large number of variables were examined, some that could be relevant to Activation time were not considered, such as cultural and clinical follow-up

factors, which may justify the variance in our multivariate model. Data about socioeconomic status were not collected.

Over 98% of the study population was Caucasian/European. Therefore, the conclusions of the present study should be limited to this ethnical group. In addition, the failure to track mortality means that the long-term consequences of delays in Activation time by sex and age cannot be accurately measured. However, in-hospital mortality is available, allowing us to observe the initial trend in these groups.

CONCLUSIONS

In summary, our study showed that STEMI times for primary PCI are longer in elderly patients and women, especially when they received their FMC outside an ED. This may be because these groups present an atypical clinical picture or ECG. The predictors of delay in activation time are age >65 years old and having a prior FMC before going to the ED. Moreover, there is no association between sex and age in patients under 65 years old with respect to activation time. However, in the case of patients over 65, women were observed to have a longer activation time. This study opens up a possible line of research focusing on STEMI in women over 65 years old, specifically analysing their clinical presentation and delays in treatment, particularly regarding activation time. In addition, continuous training, considering sex and age, of emergency doctors and nurses, would be a useful tool to improve STEMI diagnosis and treatment. With this in mind, future prospective studies should be designed and conducted to analyse the impact of these factors on delays and clinical outcomes.

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TABLES AND FIGURES

Figure 1. STEMI response times in patients admitted to the Emergency Department

Figure 1. ECG: Electrocardiogram. ED: Emergency Department. FMC: First medical contact

Figure 2. Flow chart. Population included in the study

Figure 2. ED: Emergency Department. MI: myocardial infarction. HSCSP: Hospital Santa Creu i Sant Pau

Figure 3. Graph of the activation time (min) by sex and age.

Figure 3. Figure shows the distribution of activation time according to age (< or >65 y.o.) and sex (woman vs. mean). Activation time is higher at age >65, especially in women. Graphs shows mean and standard deviation. ED: Emergency Department. Min: minutes.

ASSOCIATION OF SEX AND AGE AND DELAY PREDICTORS ON THE TIME OF PRIMARY ANGIOPLASTY ACTIVATION FOR MYOCARDIAL INFARCTION PATIENTS IN AN EMERGENCY DEPARTMENT.

ABSTRACT

Background: Time between Emergency Department (ED) and ST-segment elevation acute myocardial infarction (STEMI) activation time is a good indicator of ED quality. STEMI delays are of particular importance in some subgroups, such as women and the elderly.

Objective: To determine the association of sex and age with activation time in STEMI patients admitted to the ED.

Methods: An observational retrospective study was conducted including all patients admitted to the ED activated as a STEMI. The main variable was activation time. To evaluate the independent predictors of activation time, a multivariate logistic regression analysis was carried out, variables were sex, age, sex and age combined, chest pain, ST elevation in the electrocardiogram, and first medical contact (FMC) at the hospital's ED.

Results: A total of 330 patients were included. They were classified by sex: 23.9% (78) women and 76.1% (249) men; and age: 51.1% (167) <65 yo and 48.9% (160) ≥65 yo. Women and elderly patients exhibited a more atypical presentation. Multivariate analysis shows that showed that elderly age (OR=1.976 95%; CI=1.257-3.104; **p=0.003**) and FMC prior to attending the ED (OR=1.762; 95% CI=1.117-2.779; **p=0.015**) were associated with a longer activation time. Women older than 65 years old showed the longest activation time.

Conclusion: STEMI delays are longer in women and the elderly with atypical presentation. Age ≥65 and FMC outside the ED were associated with an increase in the activation time. This highlights the need to develop strategies to improve activation time for these specific patient groups.

Keywords: Sex, Age, STEMI, Emergency Department, Acute Coronary Syndrome, Myocardial infarction

ABBREVIATIONS LIST

CAD: Coronary Artery Disease

CRA: Cardiorespiratory Arrest

DLP: Dyslipidaemia.

DM: Diabetes Mellitus.

ECG: Electrocardiogram

ED: Emergency Department

ESC: European Society Of Cardiology

FMC: First Medical Contact

GPC: General Poor Condition.

HTA: Arterial Hypertension

IC: Interventional Cardiology

Min: Minutes

PCI: Percutaneous Coronary Intervention

STEMI: St-Segment Elevation Acute Myocardial Infarction

Yo: Years Old

INTRODUCTION

Early diagnosis and treatment of ST-segment elevation acute myocardial infarction (STEMI) are fundamental and time delays have a direct impact on subsequent mortality and morbidity.[1] Diagnosis and activation of primary percutaneous coronary intervention (PCI) for STEMI can be performed by out-of-hospital emergency services, primary care, hospitals without primary PCI capacity or directly by the Emergency Department (ED) of a hospital with primary PCI capacity. Patients attending a PCI centre had a lower Door-to-balloon time than those attending a non-PCI centre and, consequently, lower in-hospital mortality.[2]

Patients who go by themselves to the ED of a hospital with primary PCI capacity experience a longer delay than patients who contact the emergency medical services by directly calling the emergency number.[3]

The time between arrival at the ED and activation of primary PCI for STEMI is a good indicator of the quality of ED services. The STEMI clinical guidelines of the European Society of Cardiology (ESC) recommend an interval between first medical contact (FMC) and electrocardiogram (ECG) of less than 10 minutes (min), and an interval between diagnosis and balloon angioplasty of less than 60 min when the patient attends the ED of a hospital with primary PCI capacity.[4]

Also, there are several sociodemographic and clinical factors that increase the delay in STEMI treatment, such as sex (women), age (elderly), diabetes, non-smoking habit, previous cardiac history, atypical clinical and electrocardiographic presentation and unstable medical condition that requires stabilization.[5,6]

Furthermore, other research highlighted the persistence of a sex and age gap as regards STEMI diagnosis and treatment. Women receive later, inadequate treatment and their

mortality rate is higher.[7-12] Likewise, elderly patients are underdiagnosed and inadequately treated, resulting in a worse prognosis and survival rate.[13-15] For both groups, this delay is primarily attributed to the atypical signs and symptoms presented by women and elderly patients.[16–17]

There were previous records available that analysed the association of sex and age with STEMI delays and even the combination of both, but they did not specifically focus on the time between arrival at the ED and activation of primary PCI in STEMI patients admitted and diagnosed in the ED of a hospital with primary PCI capacity.[18,19] Moreover, it is unknown whether the two factors in combination multiply the delays in activation time.

The hypotheses were:

- Response times in STEMI patients who directly attend the ED of our hospital with primary PCI capacity are elevated.
- Women and the elderly who attend the ED of our hospital present a more atypical/infrequent clinical condition, which carries a greater diagnostic difficulty.
- Sex and age are predictors of delay in Activation time and time between FMC and STEMI activation.
- Given that sex and age increase delays in STEMI, jointly, both multiply the delay in Activation time.

The main objective of the study was to determine the association of sex and age with activation time in patients admitted to the ED of a hospital with primary PCI capacity and activated as a code STEMI.

The specific objectives were to identify the predictors of delay on the activation time and evaluate whether being a woman and older multiplied the ED–activation delay.

METHODS

Study design and setting

This was an observational retrospective study conducted at a hospital with primary PCI capacity between January 2013 and January 2017. The Interventional Cardiology (IC) Unit of the Hospital de la Santa Creu i Sant Pau (HSCSP) in Barcelona (Spain) provides STEMI cover to a population of 1,253,266 inhabitants, providing 24-hour cardiac catheterization facilities since 2006, and has formed part of the *Codi IAM* network of the Catalan Healthcare System since 2009. The study population was composed of consecutive patients who meet the inclusion and exclusion criteria, with suspected STEMI activated as code STEMI by the ED of our hospital. Inclusion criteria were: patients ≥18 years old, admitted to the ED of the hospital. All patients who had a first medical contact outside the ED without a clear STEMI diagnosis and were then admitted to the ED for a final diagnosis were also included. Exclusion criteria were: patients identified as STEMI in other hospitals without primary PCI capacity or in primary care centres and activated as code STEMI because these patients bypassed the ED. Patients who did not undergo coronary angiography and pregnant women were also excluded.

The total population of patients activated as a STEMI in the hospital within the study period was 1,687. Of these, 330 were patients activated from the ED of the hospital itself, meeting the inclusion/exclusion criteria. Three of these patients were excluded: two patients died before arriving at the interventional cardiology (IC) unit, and one had an alternative diagnosis immediately after being activated as code STEMI, which was immediately deactivated. This resulted in a final sample of 327 patients. In order to determine the association of sex and age with STEMI diagnosis and treatment times, the sample was divided into two groups: sex (male and female) and age (<65 and ≥65). The

age group was established based on the average age of the whole sample, which was 64±14. All variables were compared between these groups.

The study was approved by the Clinical Research Ethics Committee of the hospital (IIBSP-IAM-2015-84, IIBSP-IAM-2015-84v2) and conducted in accordance with the Declaration of Helsinki.

The primary outcome was sex and age-based differences in Activation time, that is the time between ED arrival and primary PCI activation, defined as the time to call the IC team (≤ 10 min was optimal).[2] Additionally, another outcome of interest included sex and age-based differences in FMC–Activation time, that is the time from FMC to time of the call to the IC team. The FMC was the initial contact with health professionals capable of obtaining and interpreting an ECG and performing the initial interventions outside the ED, but who had not been diagnosed and activated as a STEMI before arrival at the ED. An adequate FMC–Activation time was considered the same as the Activation time.

Other time variables were also collected and analysed. Pain time was defined as the time from the onset of symptoms and/or events. ECG time was defined as the time to perform and interpret the ECG. ED time was defined as the time from arrival at the ED of the hospital where the study was conducted and balloon time was defined as wiring of the culprit lesion. All time variables were measured in minutes. (**Figure 1) (Table2)**.

Main clinical variables and comorbidities, all-cause in-hospital mortality, hospital stay (in days, day 1 being the day of admission to the ED of our hospital until discharge), and false STEMI positives were also recorded. False positives were defined according to a) angiographic definition, which includes patients without a culprit coronary artery, and b) clinical definition, which includes patients with a discharge diagnosis other than STEMI.[20]

The criteria used to identify STEMI patients were the presence of symptoms or signs (ECG) indicating myocardial ischemia. Regarding the symptomatology, persistent oppressive chest pain with or without irradiation to the left arm, neck and jaw were considered typical and abdominal, scapular, back and nonspecific pain, dyspnea, fatigue, malaise, nausea/vomiting and syncope as atypical.[4]

As for the signs, a typical electrocardiogram was defined, as per current guidelines, as ST elevation in two contiguous leads (> 2 mm for men and 1.5-1 mm for women) and atypical as an ECG with no clear ST-segment elevation considered apt for PCI in patients with ongoing symptoms consistent with myocardial ischemia. Therefore, patients with the following electrocardiographic presentations were included: left bundle branch block, right bundle branch block, ventricular paced rhythm, isolated posterior myocardial infarction, ischemia due to left main coronary artery occlusion or multivessel disease with ST depression ≥1 mm in eight or more surface leads coupled with ST-segment elevation in a VR and/or V1 and hyperacute T waves, which may precede ST segment elevation.[4]

Data collection

All clinical variables were gathered retrospectively using the Data Collection Register, based on the recommendations of the ESC clinical guidelines.[2] The symptoms were included based on the clinical records drafted by the ED doctor, cardiologist, ED and IC nurses. The time variables were recorded prospectively by the IC on-call team and transferred to the registry network of the Catalan Healthcare System (*Codi IAM*), which is regularly audited. Moreover, all the data was collected from the information terminal of the code STEMI registry, a database containing all the clinical variables and response times belonging to the *Codi IAM* Catalan Emergency STEMI Care network.

Statistical analysis

We calculated the sample size by considering the activation time. Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a one-sided test, 22 subjects were necessary in the male group and 74 in the female group to discriminate a difference ≥ 6 minutes as statistically significant. The common standard deviation was assumed to be 9.43. A drop-out rate of 10% was anticipated. This determination was made based on the results of Dreyer RP *et al.*[18] The calculation was performed with the Granmo sample size calculator v.7.21.

The sampling technique was non-probabilistic and consecutive. A descriptive analysis was conducted, using absolute number and percentage for categorical variables, as well as mean value with standard deviation for quantitative variables with a normal distribution, and median with interquartile range for quantitative variables with a non-normal distribution. Categorical variables were compared using the Chi-squared test or Fisher's exact test, as applicable, while the quantitative variables were compared with the ANOVA or Mann-Whitney U test, depending on their distribution.

To evaluate the independent predictors of activation time, a multivariate logistic regression analysis was carried out, with all variables with $p<0.10$ in the univariate analysis being entered in order to minimize any confounding factors. To evaluate the independent predictors of the activation time, a multivariate logistic regression analysis was carried out, with all variables with $p<0.10$ in the univariate analysis being entered in order to minimize any confounding factors. The variables taken into consideration were sex, age (<65 and ≥65 years), sex and age combined, smoking, chest pain at presentation, elevation of the ST-segment in the ECG, and FMC at the ED of the hospital under study. Moreover, a multivariate logistic regression analysis was conducted to evaluate the predictors of FMC and activation time. The variables taken

into consideration were the patient's sex, age (<65 and ≥65 years), sex and age combined, smoking, chest pain at presentation, ST-segment elevation in the ECG, and FMC at the ED of the hospital under study.

To validate the logistic regression model with the dependent variable Activation time, the statistical method of Hosmer and Lemeshow revealed a value of p=0.991. Additionally, the AUC value was calculated, with a result of 0.605 (p=0.001). For the FCM-Activation time variable, the Hosmer and Lemeshow test revealed a value of p=0.998 and the AUC value was 0.752 ($p < 0.001$).

A 2-tailed level of significance of 5% ($\alpha=0.05$) was used. All analyses were conducted using the IBM–SPSS (V22.0) statistical package.

RESULTS

Study population

The final sample was 327 patients. In 75.23% (n=246) of cases, a primary PCI was carried out and 12.8% (n=42) of the STEMIs activated were false positives. The sample was divided into groups by sex, 23.9% women (n=78) and 76.1 men % (n=249), and also age, with 51.1% (n=167) in the <65 group, and 48.9% (n=160) in the ≥65 group (**Figure 2**).

Women who suffered a STEMI tended to be older than the men and more often presented atypical symptoms. **(Table 1)**.

Elderly patients had a great number of cardiovascular risk factors and comorbidities, compared with younger patients, with atypical symptoms, and presented a more serious condition on arrival at the hospital, with a more advanced Killip Class. **(Table 1)**.

In-hospital all-cause mortality was 11.6% (n=38). A multivariate analysis of the clinical factors related to in-hospital mortality was performed obtaining significant results for arterial hypertension, (OR=3.102; 95% CI=1.111–8.662; p=0.031) smoking, (OR=3.828; 95% CI=1.484–9.877; p=0.006) and Killip IV (OR=11.289; 95% CI=2.97–42.901; p<0.001).

Outcome data (Table 2)

The activation and the FMC–Activation times were longer in elderly vs. younger patients. On the contrary, FMC–activation was longer in women vs. men, but activation time did not show any differences according to sex. The longest time was detected in women > 65 years old. **(Figure 3)**.

When considering the activation time, the univariate analysis showed that age > 65 yo (**p=0.010**) and FMC outside the ED (**p=0.049**) were associated with the longer time; at

the multivariate analysis, age > 65 yo (OR=1.976; 95% CI=1.257- 3.104; **p=0.003**) and FMC outside the ED (OR=1.762; 95% CI=1.117-2.779; **p=0.015**) were independent predictors of a longer activation time. **(Table 3)**.

When considering the FMC–activation time, the univariate analysis showed that sex (female) (**p=0.026**), age (>65 yo) (**p=0.007**), sex and age interaction (**p=0.006**), atypical chest pain (**p<0.001**), atypical electrocardiogram (**p<0.001**) and FMC outside the ED (**p<0.001**) were associated with a longer delay time. However, in the multivariate analysis, only atypical chest pain (OR=2.547; 95% CI=1.343-4.831; **p=0.004**), atypical electrocardiogram (OR=3.036; 95% CI=1.542-5.979; **p=0.001**) and FMC outside the ED (OR=4.747; 95% CI=2.875-7.838; **p<0.001**) were independent predictors of a longer FMC–activation time. **(Table 4)**.

DISCUSSION

This study shows that the activation time of primary PCI for STEMI patients is longer in elderly vs. younger patients; however, it does not differ between men and women. When considering the time between FMC and activation of primary PCI, this was longer both in the elderly and women compared with younger and male patients. The study also showed that the predictors of delay in the activation time were age ≥65 and an FMC outside the hospital which did not result in STEMI identification until arriving at the ED. Lastly, there was no positive association between sex and age among patients under 65 years old, however, in patients over 65, women were observed to present a longer activation time than men.

Our results confirm other previous reports, that women and elderly patients more frequently present atypical symptoms or, in other words, less commonly present chest pain than men or patients under 65 years.[21-23] As a consequence, there was a greater delay in STEMI response times.[24,25] Therefore, to facilitate early diagnosis in the case of women and elderly patients, other atypical symptoms should be considered, such as abdominal, scapular and rib pain or general malaise/tiredness in women; and abdominal and rib pain, dyspnoea, syncope and general malaise/tiredness among elderly patients.[17,21-23] Most studies base their conclusions on the typical STEMI profile (men under 65 years old) and little attention has been focused on STEMI from the perspective of sex and age. For this reason, the most widely studied clinical profile is young men who usually present with chest pain. Various studies showed that the clinical presentation of STEMI may be different in women and elderly patients.[21-23]

In addition, some authors question the terms “typical” and “atypical” as evaluation standards, emphasizing the need for the differences to be established according to the symptomatic profiles of women and men, highlighting the need to standardize the

evaluation of symptoms but not the experience of these symptoms.[23,26,27] It is therefore essential to ensure that the sex and age perspective is included in research so that the signs and symptoms of STEMI are suitably defined.

Compared with other previous registries that analysed delays in PCI vs non-PCI centres, it was confirmed that patients attending a PCI centre had a lower Door-to-balloon time than those attending a non-PCI centre. However, in our registry, door-to-balloon time showed higher delays than in other PCI centres and higher in-hospital mortality was also observed, which could be justified as it included those who presented out-of-hospital cardiac arrest in the study population.[28]

Other authors also studied the association between sex and age related to mortality in STEMI and concluded that young women had a higher mortality, however, in our record we only observed that arterial hypertension, smoking and Killip IV were predictors of all-cause in-hospital mortality in STEMI.[29,30]

The study confirms that all STEMI diagnosis and treatment times were longer in the case of women and particularly among elderly patients, thus thorough vigilance is required in such cases.[12,14,16,25,30,31] In contrast with other studies, the primary outcome was the Activation Time of a hospital with primary PCI capacity,[18,19] because this is considered to be an indicator of optimal quality that demonstrates the ED's response capacity, thereby enabling subsequent continuous improvement strategies to be designed and implemented to enhance the healthcare quality of the hospital's ED.[32] On the other hand, although other studies compared STEMI management and outcomes between men and women, in our registry, we also established a comparison between elderly and younger patients and the association between both.[18]

Moreover, this study shows that advanced age is a predictor of a long activation time and confirms that women > 65 years present a greater delay in STEMI.[19]

This should be taken into account, especially in a pandemic situation such as COVID-19. Different registries have shown that the times for diagnosis and treatment of STEMI were higher during the pandemic,[33] which could imply a longer delay in these groups.

In contrast with other studies, when the FMC-activation data were analysed overall, neither sex nor age were seen to directly impact on the delay in this interval.[24] However, presenting atypical STEMI signs and symptoms and having a prior FMC before attending the ED were shown to be factors that increased this delay. This begs the question of whether the delay is really due to being a woman or elderly or to the atypical presentation that these groups of patients more often have.

Our study provides new data on the age and sex gap, revealing that there is no association between sex and age among young people but that, in the case of patients over 65 years old, there was a longer delay in the activation time for women.

Our registry highlights that the gap in the diagnosis and treatment of STEMI in women and the elderly persists. As suggested by other authors, bias presented by professionals associated with these groups of patients could cause the delay in FMC-balloon time.[34] It might be due to an underestimation of symptoms in these groups by ED professionals, especially when they present a more atypical or infrequent clinical picture. An automated "physician-blind" STEMI activation system, which eliminates the bias of professionals in women and the elderly, is associated with a reduction in treatment delays,[34] but it would be complex to implement in our environment and population since they are patients who come in person to the ED. Specific updating and continuous training regarding the clinical condition of women and the elderly could be a useful and feasible tool to improve the early diagnosis of STEMI in these groups and reduce the Activation time. Future research should be conducted to demonstrate the impact on activation time of education for nurses and emergency physicians in those more atypical or infrequent STEMI presentations.

And finally, as recommended by the ESC clinical guidelines, in order to ensure continuous improvement in the treatment of STEMI, regular audits must be conducted at an individual (hospital) and collective level (STEMI healthcare network), with studies being designed to enable quality of care and clinical outcomes to be monitored according to sex and age, to improve these parameters and eliminate the differences that exist in our setting.

LIMITATIONS

Retrospective data collection presents limitations due to its single-hospital and retrospective design, thus the results for Activation time and FMC-Activation time delays can only generate hypotheses for the factors that could contribute to reducing STEMI response times. In this study, this issue was minimized because standardised records were available and implemented throughout the entire National Healthcare System. The registration form used was specifically for the Catalan Public Healthcare System, however, many of the items contained are common to the forms used by other national and international registries and, therefore, their results were comparable. Another limitation could be that the data collected represents a picture of the population and Health Care System from between 2013 and 2017, which could be argued to be different nowadays. However, since 2013, there has not been an active consciousness campaign for ED healthcare workers in terms of clinical presentation and how to proceed in women and the elderly and, therefore, even if the global time delays might be better now, we do not believe there has been any change in these special groups.

And finally, although a large number of variables were examined, some that could be relevant to Activation time were not considered, such as cultural and clinical follow-up

factors, which may justify the variance in our multivariate model. Data about socioeconomic status were not collected.

Over 98% of the study population was Caucasian/European. Therefore, the conclusions of the present study should be limited to this ethnical group. In addition, the failure to track mortality means that the long-term consequences of delays in Activation time by sex and age cannot be accurately measured. However, in-hospital mortality is available, allowing us to observe the initial trend in these groups.

CONCLUSIONS

In summary, our study showed that STEMI times for primary PCI are longer in elderly patients and women, especially when they received their FMC outside an ED. This may be because these groups present an atypical clinical picture or ECG. The predictors of delay in activation time are age >65 years old and having a prior FMC before going to the ED. Moreover, there is no association between sex and age in patients under 65 years old with respect to activation time. However, in the case of patients over 65, women were observed to have a longer activation time. This study opens up a possible line of research focusing on STEMI in women over 65 years old, specifically analysing their clinical presentation and delays in treatment, particularly regarding activation time. In addition, continuous training, considering sex and age, of emergency doctors and nurses, would be a useful tool to improve STEMI diagnosis and treatment. With this in mind, future prospective studies should be designed and conducted to analyse the impact of these factors on delays and clinical outcomes.

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TABLES AND FIGURES

Figure 1. STEMI response times in patients admitted to the Emergency Department

Figure 1. ECG: Electrocardiogram. ED: Emergency Department. FMC: First medical contact

Figure 2. Flow chart. Population included in the study

Figure 2. ED: Emergency Department. MI: myocardial infarction. HSCSP: Hospital Santa Creu i Sant Pau

Figure 3. Graph of the activation time (min) by sex and age.

Figure 3. Figure shows the distribution of activation time according to age (< or >65 y.o.) and sex (woman vs. mean). Activation time is higher at age >65, especially in women. Graphs shows mean and standard deviation. ED: Emergency Department. Min: minutes.

Figure 1. Response times in STEMI in patients admitted in Emergency Department

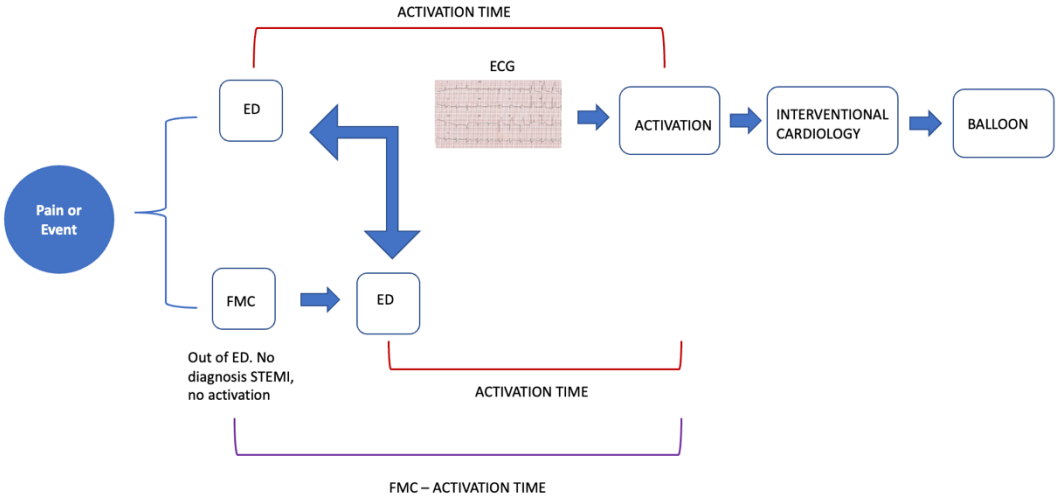

Figure 1. ECG: Electrocardiogram. ED: Emergency Department. FMC: first medical contact

Figure 2. Flow chart. Population included in the study

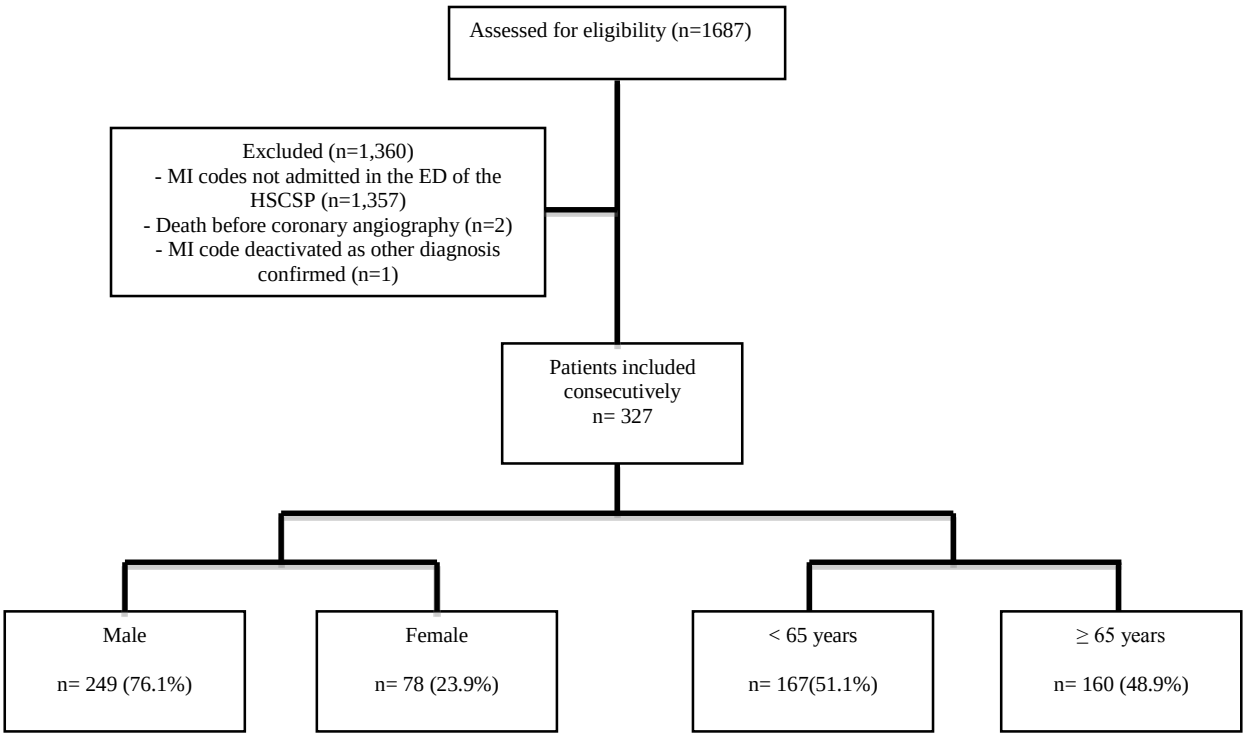

Figure 2. ED: Emergency Department. MI: myocardial infarction. HSCSP: Hospital Santa Creu i Sant Pau

Figure 3. Graph of the activation time (min) by gender and age.

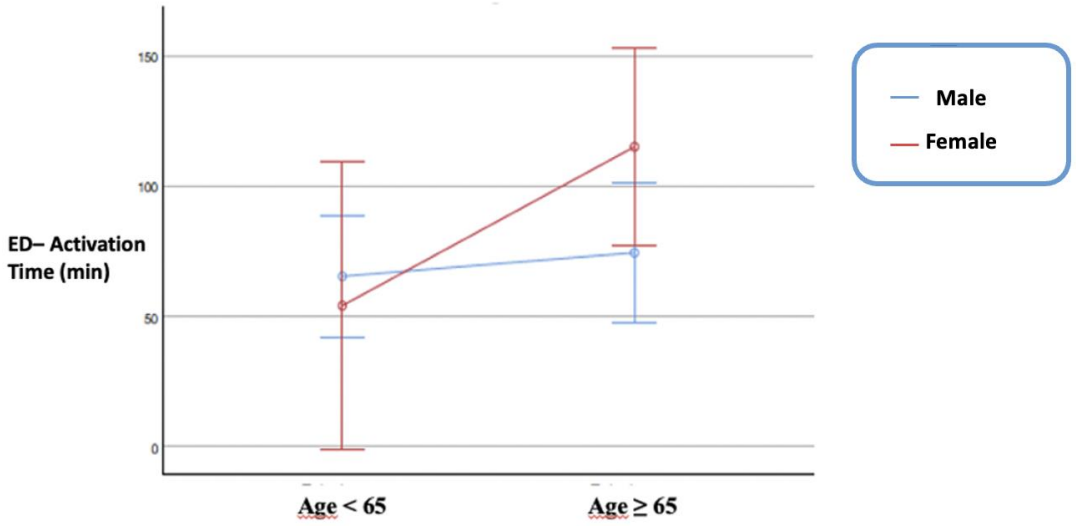

Figure 3. Figure shows the distribution of activation time according to age (< or >65 y.o.) and to gender (woman vs. Mean). Activation time is higher at age >65, especially in woman. Graphs shows mean and standard deviation. ED: Emergency Department. Min: minutes.

Table 1. Baseline clinical characteristics of study participants result variables.

Variables	STEMI Code n= 327 (100%)	Male 249(76.1)	Female 78(23.9)	p	<65 years 167(51.1)	≥65 years 160(48.9)	p
Male gender	327(100)	249(76.1)	0		142(85)	107(66.9)	<0.001
Age	64±14	61.93±13.4	71.59±13.6	<0.001	167(51.1)	160(48.9)	
HTA	198(60.6)	147(59)	51(65.4)	0.317	86(51.5)	112(70)	0.001
DLP	177(54.1)	136(54.6)	41(52.6)	0.751	80(47.9)	97(60.6)	0.021
DM	84(25.7)	67(26.9)	17(21.8)	0.367	36(21.6)	48(30)	0.081
Tobacco use	196(59.9)	175(70.3)	21(26.9)	<0.001	121(72.5)	75(46.9)	<0.001
Obesity	63(19.3)	45(18.1)	18(23.1)	0.336	37(22.3)	26(16.3)	0.167
CAD	80(24.5)	58(23.3)	22(28.2)	0.379	30(18)	50(31.3)	0.005
Killip III/IV	58(19.9)	40(16.1)	18(23.1)	0.119	19(11.4)	39(24.4)	<0.001
FMC ED	184(56.3)	143(57.4)	41(52.6)	0.450	107(64.1)	77(48.1)	0.004
Working hours	120(36.7)	96(38.6)	24(30.8)	0.213	59(35.3)	61(38.1)	0.600
PCI	249(75.9)	193(77.5)	55(70.5)	0.208	128(76.6)	120(75)	0.728
ECG ST elevation	267(81.7)	202(81.5)	64(83.1)	0.741	145(86.8)	121(76.6)	0.017
Chest pain	254(77.4)	200(80.3)	54(70.1)	0.060	141(84.4)	113(71.1)	0.004
Epigastric pain	37(11.3)	26(10.5)	11(14.3)	0.359	17(10.2)	20(12.7)	0.482
Abdominal pain	12(3.7)	6(2.4)	6(7.8)	0.029	3(1.8)	9(5.7)	0.062
Scapular pain	22(6.7)	11(4.4)	11(14.3)	0.003	11(6.6)	11(7)	0.893
Rib pain	7(2.1)	3(1.2)	4(5.2)	0.035	1(0.6)	6(3.8)	0.047
Back pain	28(8.6)	16(6.5)	12(15.6)	0.013	21(12.6)	7(4.4)	0.009
Dyspnoea	71(21.8)	50(20.2)	21(27.3)	0.187	24(14.4)	47(29.7)	0.001
Syncope	19(5.8)	13(5.2)	5(6.5)	0.675	5(3)	13(8.2)	0.039
GPC/Weakness	46(14.1)	28(11.3)	18(23.4)	0.008	17(10.2)	29(18.4)	0.035
CRA	36(11)	31(12.5)	5(6.5)	0.142	16(9.6)	20(12.7)	0.377
In-hospital mortality	38(11.6)	28(11.2)	10(12.8)	0.689	10(6)	28(17.5)	0.001
Hospital stay	5(3–8)	5(3–8)	5(3–9.75)	0.527	4(3–7)	5(3–10.25)	0.002
False positive	42(12.8)	35(14.1)	7(9)	0.242	23(13.8)	19(11.9)	0.608

- **Table 1.** The figures show n (%). Mean ± standard deviation. CAD: coronary artery disease. CRA: cardiorespiratory arrest. DLP: dyslipidaemia. DM: diabetes mellitus. ECG: electrocardiogram. ED: Emergency Department. FMC: first medical contact. GPC: general poor condition. HTA: arterial hypertension. PCI: percutaneous coronary intervention.

Table 2. Time of STEMI activation in acute myocardial infarction.

Time Variables	Total STEMI	Male	Female	p	<65 years	≥65 years	p
No. of patients	327 (100)	249(76.1)	78(23.9)		167(51.07)	160(48.93)	
Activation time	30(15–69)	30(14–60)	33(15.75–124.25)	0.134	26(14–50)	36(15–93.25)	0.029
FMC–Activation time	51(26–110)	50(25–98)	69·5(29.5–161.25)	0.049	45(23–88)	63(31–135.5)	0.008
Pain–FMC time	80(25–180)	83(25.2–175)	62.5(19.8–241.5)	0.811	73(30–165)	88(20–230)	0.903
FMC–ECG time	10(5–26)	10(5–25)	12(5–32.5)	0.221	10(5–20)	12(5–35)	0.036
ECG–Activation time	30(12–75)	26(11–70)	33(15–98.5)	0.095	25(10–64)	31.5(14.3–90)	0.224
Activation–IC time	30(20–35)	30(17–37)	30(23.8–35)	0.610	29(16–35)	30(20–35.8)	0.301
ECG–Balloon time	88(65–132)	85(65–120)	93(70–165)	0.137	77(62.3–115)	94(72.3–147.5)	0.004
IC–Balloon time	25(20–31)	25(20–30)	29(20–35)	0.021	25(20–30)	26(20–33)	0.120
ED–Balloon time	88(65–121)	85(62–117.5)	94(74–173)	0.058	76.5(60–105.8)	102.5(74.3–140.5)	<0.001
FMC–Balloon time	109(77–160)	106(75.5–155.5)	120(85–190)	0.141	95(70.5–145.8)	120(93.3–183.8)	0.001
Pain–Balloon time	207(135–400)	203(133–339.5)	240(152–535)	0.138	188.5(125–329.5)	236.5(154–466.3)	0.051

The table shows n (%) Median (interquartile range). Time intervals: minutes (min). ECG: electrocardiogram. ED: Emergency Department. FMC: first medical contact. IC: interventional cardiology.

Table 3. Predictive factors of delay in Activation time for STEMI patients

Variables	Univariate Regression ED–activation			Multivariate Regression ED–activation		
	OR	95% CI	p-value	OR	95% CI	p-value
Gender	1.096	(0.659 – 1.823)	0.725			
Age (<65 vs ≥65)	1.783	(1.151 – 2.764)	0.010	1.976	(1.257 – 3.104)	0.003
Age x gender	1.538	(0.848 – 2.790)	0.156			
Chest pain	1.374	(0.812 – 2.325)	0.237			
ECG ST elevation	1.620	(0.914 – 2.872)	0.098			
FMC ED	0.643	(0.414 – 0.998)	0.049	1.762	(1.117 – 2.779)	0.015

CI: confidence interval. ECG: electrocardiogram. ED: Emergency Department. FMC: first medical contact. OR: odds ratio

Table 4. Predictive factors of delay in FMC–Activation time for STEMI patients

Variables	Univariate Regression FMC–Activation			Multivariate Regression FMC–Activation		
	OR	95% CI	p-value	OR	95% CI	p-value
Gender	1.805	(1.074 – 3.035)	0.026			
Age (<65 vs ≥65)	1.831	(1.181 – 2.840)	0.007			
Age x gender	2.380	(1.276 – 4.441)	0.006			
Chest pain	3.594	(2.013 – 6.417)	<0.001	2.547	(1.343 – 4.831)	0.004
ECG ST elevation	3.221	(1.728 – 6.003)	<0.001	3.036	(1.542 –5.979)	0.001
FMC ED	5.377	(3.330 – 8.683)	<0.001	4.747	(2.875 – 7.838)	<0.001

CI: confidence interval. ECG: electrocardiogram. ED: Emergency Department. FMC: first medical contact. OR: odds ratio