Universitat de Girona

FINAL DEGREE PROJECT

IMPACT OF THE COVID-19 LOCKDOWN ON ISCHAEMIC HEART DISEASE

BEFORE-AND-AFTER OBSERVATIONAL STUDY

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1. ABBREVIATIONS

AMI	Acute Myocardial Infarction
CABG	Coronary Artery Bypass Graft surgery
CAP	Centre d'Atenció Primària (Primary healthcare centre)
CEIC	Comitè d'ètica d'investigació Clínica
ECG	Electrocardiogram
EMS	Emergency Medical Services
FMC	First Medical Contact
ICU	Intensive Care Unit
LVEF	Left Ventricular Ejection Fraction
NSTEMI	non-ST-segment elevation myocardial infarction
OHCA	Out-of-Hospital Cardiac Arrest
PCI	Percutaneous Coronary Intervention
PPE	Personal protection equipment
SEM	Sistema d'Emergències Mèdiques (EMS)
STEMI	ST-segment elevation myocardial infarction
WHO	World Health Organization

2. ABSTRACT:

Background: The onset of the COVID-19 pandemic had a huge impact on our society, even the healthcare system had to adapt to the new circumstances. The online access to healthcare centres became easier, but the barriers between physicians and patients were multiplied. Many interventions and consultations were delayed for many months with the purpose of reducing the contagion. Nevertheless, some pathologies cannot be postponed, they must be diagnosed and treated immediately. One of them is heart ischaemic disease, which is the main cause of mortality worldwide. Different studies around the globe have already shown a change in its tendencies: decrease in hospital admissions, increase in mortality, and treatment delay, among others.

It is known that we will keep having outbreaks until a treatment or a vaccine are found, so we might end up in a similar situation very soon. Knowing exactly which procedures were altered during the National quarantine in our environment is the first step to prevent them from malfunctioning again in the next lockdown.

Objectives: The main objective is to determine whether there is an increase in time-to-reperfusion of STEMI during and after the COVID-19 lockdown compared to the same periods in the previous year in Girona.

The secondary objective is to determine whether there is a decrease in the accumulated incidence of STEMI during and after the COVID-19 lockdown compared to the same periods in the previous year in Girona.

Methodology: It is a before-and-after observational study using a population-based AMI registry, the *registre Codi IAM*. We will compare time-to-reperfusion, incidence and mortality in Girona between the COVID-19 lockdown, the following period until the next outbreak, and the same periods the year before by the corresponding analysis of variance, Poisson regression and Cox Proportional-Hazard. The 3 analysis will be stratified by covariates.

Participants: All the STEMI occurred in Girona and treated in the *Hospital Dr Josep Trueta* during the 4 periods

Keywords: STEMI, lockdown, time-to-reperfusion, delay

3. INTRODUCTION

Our society has gone through a tough period during the last months. The arrival of coronavirus has changed the way we used to live, work, and communicate, among others. Our healthcare system is not an exception, it has had to adapt to the new circumstances.

During the period of coronavirus quarantine between the months of March and May, the use of telemedicine overtook the face-to-face visits in Catalonia as well as in many other parts of the world (1,2). It enabled the maintenance of the primary care whereas reducing the spread of the virus. Not only do telemedicine have benefits, but it also has some limitations, such as the impossibility of physical examination or the difficulty of ensuring all the required parameters in order to achieve the necessary doctor-patient relation (3). These disadvantages, without the support of face-to-face care, may lead to the underdiagnosis of many diseases and disorders, especially in the first-time visit, however, the previous built relation with already known patients can make it easier(4).

In addition, the fear of being infected prevents the patients from demanding help for reasons they would have asked before, but now they do not dare to. The delay of the consultation may lead to a worse stage at diagnosis, consequently, a less effective treatment and a worse outcome.

Even though the lockdown finished in our country, new cases are appearing day after day. Finding which diseases went unnoticed could come in handy to prevent them from worsening again in case we end up in another quarantine. Studying all of them at once may be impossible. Taking into account that cardiovascular diseases are the most prevalent cause of death in our society(5), they should be a primary priority.

3.1. CORONAVIRUS PANDEMIC

In December of 2019 the correspondent authorities in Wuhan (Hubei, China) admitted having many cases presenting pneumonia of unknown aetiology related to a market in the mentioned city, the Huanan Seafood market, which had to be closed on the 1st of January. It was not until the 5th of January of 2020 when the WHO declared the outbreak, whereas the Chinese authorities were trying to seek

the close contacts, researching the cause, and sanitizing infected areas. Eventually, on the 7th of January, the novel coronavirus was identified (6).

The virus spread from China to Thailand, on the 13th of January, and after that it kept on spreading worldwide, consequently, the WHO had to declare the pandemic on the 11th of March of 2020 (6).

The first COVID-19 case in Spain was found on the 31st of January in the Canary Islands, but the virus did not reach the peninsula until the 24th of February, when it started spreading gradually (7).

The increase in COVID-19 cases in the country made the government take measures in order to lower the speed of the contagion (shortening the curve's height) and to avoid collapsing the healthcare system. In Catalonia, the *Pla de Protecció Civil de Catalunya* cancelled crowded events and started limiting the capacity in closed spaces on the 12th of March. The Spanish government approved the state of alarm on the 14th of March with the aim to last for 2 weeks, but after 6 extensions, it prevailed until the 21st of June(8). The measures taken with the aim of reducing the spread of the virus were based on social distancing, so that freedom of movement was limited, and everyone was confined at home, except for the essential workers(9).

While schools, shops and streets were getting emptier, the hospitals around the country were getting more and more crowded with people suffering from COVID-19, some of the hospitals even collapsed. Many measures were taken so as to prevent it. Surgeries, consultations and all the other activities that did not urge were delayed. Many rooms with different purposes were turned into ICUs so that many hospitals notably multiplied the number of beds and respirators(10).

In-person consultations were reduced between the 55% and the 79% in primary care, whereas the telemedicine increased between the 70% and the 100% (1).

3.2. ISCHAEMIC HEART DISEASE:

3.2.1. Definition

Acute myocardial infarction (AMI) defines the presence of myocardial injury demonstrated by an elevated cardiac troponin value (>99percentile), and necrosis in a clinical context suggesting myocardial ischaemic (11).

It can be classified in 3 main types, depending on the characteristics accompanying the clinical manifestations (11):

- STEMI: ST-segment elevation myocardial infarction
- NSTEMI: non-ST-segment elevation myocardial infarction
- Unstable angina: non- ST-segment elevation and negative troponin

3.2.2. Epidemiology:

The ischaemic heart disease is the most prevalent cause of dead all around the world(11), including Spain (5). Not only has the incidence increased worldwide during the last years, but the mortality has also gone up, aside from Europe, where fatality has decreased(11).

The incidence is not following the same course in all the subtypes, as STEMI is decreasing and NSTEMI is increasing.

3.2.3. Cardiovascular risk factors:

Risk factors can be divided in two groups. On the one hand, there are the non-modifiable factors, as the name implies, they are inherent to the individual and cannot be changed. They are age, sex and genetics (12).

On the other hand, there are the modifiable factors. These are the ones that can be prevented or treated in order to reduce cardiovascular risk. They are smoking, high blood pressure, diabetes mellitus, obesity, and hypercholesterolemia. Other factors may interact with these ones, improving or worsening the global risk if they are not followed, as the physical exercise and the Mediterranean diet (12).

3.2.4. Diagnosis:

The diagnosis must be done in the first medical contact (FMC). There are 2 possible presentations. The typical and the most common appears with a thoracic pain that has lasted at least for 20 minutes and has no response to nitro-glycerine. The pain can irradiate from the thorax to the left arm, the neck, or the jaw. The less common presentation, so-called atypical, is characterized by a latest onset and the following symptoms: nausea and vomit, fatigue, palpitation, dyspnoea, or syncope(13).

An ECG should be done within 10 minutes to discover if there is an ST-segment elevation measured in the J point in 2 consecutive derivations. The ST-segment elevation is considered in the following cases (13):

- Men under 40y: ≥0,25mV
- Men over 40y ≥0,2mV
- Women: ≥0,15mV in V2-V3 or ≥0,1mV in others without hypertrophy of the left ventricle nor bundle branch block

If there is an ST-elevation, the AMI is a STEMI. If it is not the case and it remains without the elevation, it declines instead or there are changes in the T wave, it is a NSTEMI or an unstable angina(14,15). A normal ECG does not discard a NSTEMI, but the test should be repeated in 6 -24h (14).

After the ECG, the patient can be monitored with a defibrillator. Having defibrillator equipment around is useful since ventricular fibrillation can cause a heart arrest in the early hours and it may occur out of the hospital (11). Blood sampling should be done if it does not mean any delay(11). It will help determine the troponin levels. High levels mean myocardial damage and suggest the presence of a STEMI or a NSTEMI (11,15). Low levels suggest an unstable angina (15).

Once in the hospital, if there are still doubts on the diagnosis, it is possible to do an urgent angiography. If the findings suggest an occlusion, it can be followed by the reperfusion, the primary angioplasty, also called percutaneous coronary Intervention (PCI) (11).

Meanwhile, other interventions should be considered, as supplying oxygen if needed, or providing intravenous opioids, not only for the analgesic effect, but also for the anxiety (11).

3.2.5. Treatment

When the diagnosis of a STEMI is made in a pre-hospital setting, it is important to get ready the catheterization laboratory(13). No sooner does the patient arrive than the coronary angioplasty will be done. Timing is extremely relevant, best results are achieved when time to treatment after diagnosis is shorter.

Reperfusion of the coronary flux with PCI is indicated within the first 120minutes after diagnosis and 12 h of the pain onset. If the pain and signs of ischaemia are still present after 12h, it is recommended too, but it is not clear whether it can have any benefits after this period in absence of any signs or pain (13).

When the PCI cannot be guaranteed within 120 minutes, thrombolytic therapy is indicated. It is not as good as the previous one, so if it is possible, a posterior PCI should be done as well (11). Results are much better when thrombolysis is done in the pre-hospital settings than in the hospital because of the saving of time. If this is the chosen treatment, it should be administrated within the first 10 minutes after diagnosis. If the treatment fails, a rescue PCI is needed as soon as possible, but if it succeeds, the PCI has to be done within 24h(16).

There are two possible treatments for NSTEMI, conservative medical therapy, and revascularization. The election must consider the risk of another cardiovascular event and the benefits of undergoing an early invasive therapy(14).

In contrast to STEMI, NSTEMI should not be treated with fibrinolytic therapy. There are two ways to perform the revascularization: PCI and coronary artery bypass graft surgery (CABG). PCI is more used, but CABG is chosen for left main disease and equivalent or in 2-3vessels disease (14). PCI is indicated in less than 24h if the risk is assessed as high, and in less than 72h if it is intermediate (15).

Heart arrest with ST-elevation should be treated with PCI, yet the ones without ST-segment elevation should be studied to look for other non-cardiac causes(11).

3.2.6. STEMI pathway (*Codi IAM*)

The need for fast diagnosis and treatment requires a system to make it possible. For this reason, there is a “STEMI pathway” that should be followed to reduce delays in treatment as much as possible. Not all the patients follow the same circuit, although there are common steps (16). The whole process can be divided into different steps that can be combined in 4 possibilities depending on the characteristics of the place where the FMC occurs. [Figure 1] The patient can call the EMS, which in Catalonia is called SEM, and wait in the place where the symptoms have started. If instead of calling, the patient goes to a healthcare centre, there are 3 possibilities. The centre might be a CAP, which is a Primary

healthcare centre, or it might be a hospital with or without catheterization laboratory, the necessary equipment to perform a PCI. It is important to know exactly which pathway has followed each patient to calculate time-to-reperfusion.

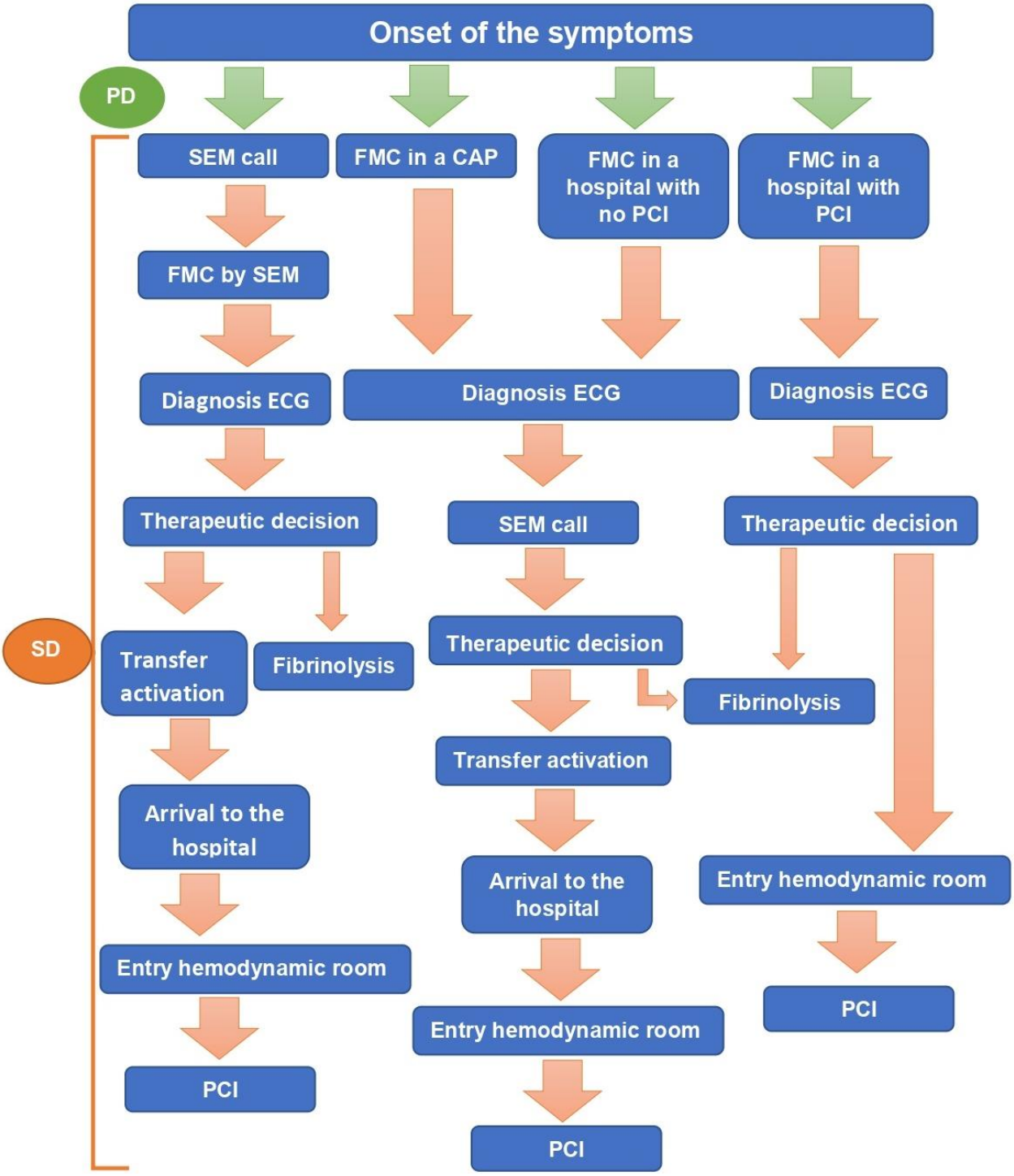

Figure 1: Diagram of the 4 STEMI pathways in Catalonia. (11,13,16,17)

PD: Patient delay; SD: System Delay; SEM: Sistema d'Emergències Mèdiques; FMC: First Medical Care; CAP: Centre d'atenció primària; ECG: Electrocardiogram; PCI: Percutaneous Coronary Intervention.

3.2.7. The importance of time-to-reperfusion

The importance of a short time-to-reperfusion has already been shown in many studies and in both treatments, thrombolytic therapy (18) and PCI. A retrospective study between 1994 and 2001 proved relation between symptom-onset-to-balloon time and mortality risk in the following year, recommending the treatment within 3h counting from the start of symptoms (19). Actually, a consecutive study shown that every 30 minutes of delay in treatment mean an increase of 7.5% in 1-year-mortaity (20).

All the steps of the above-mentioned pathway have been analysed and assigned a maximum time in minutes. If they exceed their time, they are considered to cause a delay in time-to-reperfusion.

The first step is the time that takes the patient to contact medical help. Ideally, it should be done within the first 5 minutes of symptoms, but there is usually a delay of 2 hours (16). Many factors may intervene, as health campaigns in the area or the fear of the patient of disturbing or worrying their relatives or caretakers (11,16). The length of time depends only on the patient; therefore, it is called the patient delay.

Once the contact has been done, the System delay starts. The following steps, as mentioned before, are the FMC, the diagnosis with ECG and finally the treatment. The activation of the STEMI pathway because of a suspicious ECG, should be possible 10 minutes after the FMC (16). Then, the treatment should be decided regarding the necessary time to arrive in the catheterization laboratory. If it is not possible to have the patient undergoing a PCI in less than 120 minutes, thrombolytic therapy should be applied in the prehospital setting in less than 10 minutes after diagnosis (16).

Many factors have been shown to enlarge the patient delay, such as sex, diabetes mellitus and silent infarction (21). Other factors have been proved to affect different steps of the system delay(22). The FMC out of a hospital with catheterization laboratory, the distance between the two places and the events occurred out of office hours require more time to get to the catheterization. Age was related to the delay of diagnosis and a large transfer to the hospital. The antecedents of a previous cardiac surgery of bypass, the localization of a lateral

infarction and the heart failure enlarge the process of reperfusion once in the catheterization laboratory. OHCA and cardiogenic shock have an impact on the three parts of the system delay. They complicate the diagnosis, the transfer and the treatment in the laboratory (22).

3.2.8. Prognosis:

STEMI has a higher risk of mortality in the first 30 days after the event than the NSTEMI, though this one has a higher risk of reinfarction, so mortality after one year is not dissimilar (23).

Heart failure is a common complication, and it is an indicator of poor prognosis. The ventricular disfunction can be clinically assessed using the Killip-Kimball classification or it can be measured using an echocardiography (23).

The Killip classification is one of the collected parameters of the *Codi IAM* registry, and it is assessed at the hospital admission. When the classification was invented, the 4 stages were given a mortality rate (6%,17%,38%, 81%). The treatment advances have lowered them although mortality risk is still higher for those with a higher Killip (17,24):

- Killip I: No clinical symptoms of heart failure.
- Killip II: Moderate heart failure including rales in the pulmonary bases, a third sound and an increase in jugular venous pressure.
- Killip III: Acute pulmonary edema.
- Killip IV: Cardiogenic shock, hypotension, and evidence of peripheral vasoconstriction as oliguria, cyanosis, and diaphoresis.

Cardiogenic shock, the KILLIP IV stage, is the main cause of mortality in AMI. It explains the 50% of mortality rate in the hospital. Prevention and treatment of this complication require an early reperfusion. (25)

The echocardiographic classification divides the LVEF measure as follows(23):

- Normal >50%
- Moderately impaired 40-50%
- Severely impaired <40%

LVEF at discharge is a good indicator of mortality, the lower the value, the higher mortality risk (23). Improvement of LVEF 9 months after revascularization compared with the initial value indicates a better prognosis(26).

3.3. COVID-19 AND ISCHAEMIC HEART DISEASE

3.3.1. Sharing context

The lockdown may have had an impact on ischaemic heart diseases in different aspects. Many studies have tried to assess the possible damages from different points of view.

In the first place, a decrease in the number of PCI compared with the previous years has been detected in different countries. In March, the number of PCI was reduced a 38% in the US according to an observational study made by the American college of Cardiology (27), whereas the same College states that STEMI should be treated the same way as before the pandemic. They claim that the only difference is that professionals should wear PPE now (28). A similar situation was found in Spain in the beginning of the lockdown. A poll answered by 73 hospitals all around the country showed a decrease in interventions in STEMI of the 40% and a slight increase in the fibrinolytic treatment in the period between the 16th and 22nd of March compared with the period between the 24th of February and the 1st of March (29).

In the second place, a reduction in hospital admissions for STEMI in the early lockdown has been reported in recent studies in Catalonia(30), Italy (31) and Austria (32). Some other studies have only considered STEMI treated by PCI(33) and not all patients meet the criteria to receive this treatment, therefore, the incidence might be biased.

In the third place, delays in time-to-reperfusion have been studied too. A short sample description of cases in Hong Kong shows the 2 types of delays: of the patient and the system (34). They suggest that the first delay may be due to the fear of getting infected when leaving home. However, the second one is not that clear. It could be a consequence of all the prevention measures taken to avoid the contagion, the added difficulty to access the hospitals, etc. A wider study in China shows an increase in the period between FMC and the introduction of the

wire of 20.82 minutes in Hubei and 4.43 minutes in other provinces, but declares that the impact of the outbreak on the ischaemic time was not significant(35).

Finally, a population-based, observational study shows an increase in OHCA in Paris during the quarantine compared with the previous years, with a consequent rise in death rate (36).

Other studies have tried to seek the reason why many changes occurred during the lockdown. Isolation is supposed to cause a change in habits which could worsen risk factors. Not only because of pathologic reactions as stress, depression, or anxiety, but also boredom (37). They all may change the eating habits into a less healthy diet with more junk food and less antioxidants, that together with the lack of exercise that staying at home implies may end up with weight gain and in the long term, with hypertension and diabetes mellitus or the so-called metabolic syndrome and also atherosclerosis (38).

3.3.2. Ischaemic heart diseases as a consequence of COVID-19

Being the most prevalent cause of death, cardiovascular disease is one of the most prevalent comorbidities affecting coronavirus patients behind hypertension and Diabetes Mellitus. It sems these patients, when being infected with SARSCOV2, are more likely to end up suffering from a severe COVID-19 disease and eventually death (39).

Moreover, COVID-19 itself may be related to the onset of cardiovascular diseases in patients with no previous diagnosis. There is still a lack of information but many studies have reported findings which might explain an increase in cardiovascular diseases, such as a rise in cardiac troponins in the ones who did not survive compared with the ones who did it (40), and an increase in thrombotic complications (41).

4. JUSTIFICATION

Even though the COVID-19 quarantine in Spain finished in June, getting ready for a second massive confinement is not so far-fetched, as the number of cases is going up again. In March, the pandemic caught us off guard and the health system had to face unexpected problems. In case there is a second round, all the risks and complications should be considered.

As it is mentioned earlier on this paper, many studies around the globe have found changes in different aspects related to heart ischaemic diseases compared to previous years as delay in diagnosis or decrease in hospital admissions. Even though every day there is more data, the topic is still too recent and there is not enough information to do a more precise assessment of the current situation.

It is necessary to determine whether cardiac patients had the mentioned difficulties in our area as well, as every country has applied different types of restrictions, and in a different health system. If any changes are found, the causes should be identified in order to prevent them in case of a new lockdown. For this reason, many parameters should be studied in our environment.

The main factor which will determine the sample will be the period when the cardiovascular events occurred. The variables studied during the COVID-19 lockdown of 2020 will be compared with the same period in 2019 to determine whether the National confinement meant any difference. The COVID-19 lockdown of 2020 will be compared with the following period until the next outbreak to determine if the easing of restrictions changed the results again. This last period will be compared with the same months in 2019 to ensure the results found are due to the lowering of restrictions and not just a seasonal factor.

The period including the lockdown will be limited by the length of the state of alarm in order to include the massive confinement and the following de-escalation. The posterior period will last until October, when all the cancelled activities had started again, and the cases started going up.

The comparison between the mortality rate of the 4 periods may indicate if there has been a real impact on ischaemic heart diseases. Despite the relevance of mortality as an indicator of impact on health, it may not be the best variable to study in this case. The sample of people studied will not be big enough to

guarantee a significant result. However, there are other parameters that may indicate an increase in mortality. As it has been mentioned before, time-to-reperfusion has been proved to intervene in the prognosis of a patient suffering from a STEMI, consequently, the comparison of time-to-reperfusion between the 4 periods will be studied instead. Specifically, time-to-reperfusion should be divided into patient and system delay, so that, it will be possible to discern which one is causing the delay. System delay can be split into many steps that will be studied individually in order to analyse if one of them has suffered a larger delay than the others.

Timing is more relevant in the treatment of STEMI than in the NSTEMI, where an early PCI is indicated in less than 24h. Time-to-reperfusion cannot be compared between these two types of AMI, for this reason the present study will contemplate just the STEMI, the one which causes a higher immediate mortality.

There are other factors that may help identify changes in treatment. The number of patients who underwent PCI and those who underwent thrombolytic therapy in the same periods will be compared too. A decrease in PCI may suggest a delay in diagnosis and treatment.

There are many parameters that have been described to alter time-to-reperfusion in a non-pandemic period, as it is mentioned before on this paper. These factors will be included as confusion variables to determine whether the outcomes may be explained by a change of characteristics of the patients and not by the independent variable.

Accumulated incidence of ischaemic heart events in the 4 periods will be compared so as to determine if the changes described in other countries suit our environment too. Theoretically, an increase should be found, since cardiovascular factors have been altered, as mentioned before, and a new factor has been added, COVID-19 itself. However, we expect to find a decrease in incidence, according to the previous studies.

The infection of SARS-CoV-2 will be an important covariate, since it is a distinct and new factor which only affects 2 of the 4 periods of the present study and we do not know exactly which relation it has with the AMI, as a cause or a worsening factor.

5.HYPOTHESIS:

The COVID-19 lockdown between March and June led to a delay or an underdiagnosis of ischaemic heart diseases which caused a worse outcome after treatment.

6.OBJECTIVE:

The primary objective of this study is to determine whether there is an increase in time-to-reperfusion of STEMI during and after the COVID-19 lockdown compared to the same periods in the previous year in Girona.

The secondary objective of the study is to determine whether there is a decrease in the accumulated incidence of STEMI during and after the COVID-19 lockdown compared to the same periods in the previous year in Girona.

7.METHODOLOGY

7.1. STUDY DESIGN

It is a before-and-after observational study using a population-based AMI registry, the *registre Codi IAM* (AMI Code registry).

7.2. SAMPLE

7.2.1. Sample selection

The sample will include all the STEMI occurred in Girona and treated in *Hospital Dr Josep Trueta de Girona* during the 4 periods defined as independent variables. All the subjects will be selected from the registry *Codi IAM*. This registry has the aim of following and assessing the care process of patients who may need reperfusion in 10 hospitals from Catalonia since 2010. The present study will include the patients treated only in the mentioned hospital.

Inclusion criteria: STEMI cases treated by fibrinolysis or PCI in Hospital Dr Josep Trueta

Exclusion criteria: STEMI cases happened in Girona but transferred to other hospitals

7.2.2. Sample size:

We have used an online free sample size calculator(42) to determine the necessary subjects to include in the study derived from the present protocol.

Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, 95 subjects are necessary in each of the 4 groups to recognize as statistically significant a minimum difference of 13.7 minutes between any pair of groups when comparing time-to-reperfusion. The common deviation is assumed to be 27 minutes. It has been anticipated a drop-out rate of 0% as the source for the sample is an exhaustive population registry called *Codi IAM* where all subjects are included.

The reference values have been taken from a previous research based on the same registry and in the same area (22). It was estimated that time-to-reperfusion (from ECG to artery opening) was 106.3 minutes with a deviation of 27 minutes. There were only 13.7 minutes left to reach the limit of 120 minutes. If such an increase were to occur, there would be a real change in prognosis.

In 2017 nearly 340 patients were assisted in *Hospital Dr Josep Trueta* for an AMI code(43), for this reason, and taking into account that every year the incidence exceeds the previous one, the required number of patients will be overtaken in the 4 groups.

7.3. VARIABLES

7.3.1. Dependent.

The main dependent variables are time-to-reperfusion and some of its steps. Each time frame will be measured in minutes and it will be calculated subtracting the initial and final times described in the *Codi IAM* registry in this format:

- Date: (day/month/year) (dd/mm/yyyy)
- Time: (hour/minute) (hh:mm)

The registry includes the date and time when all the actions take place. We will use the date and time of the following actions:

- Date and time of the onset of the symptoms
- Date and time of the alert to the SEM
- Date, time, place, and service of the FMC
- Date, time, and place of the first diagnostic ECG
- Date, time, and reason for fibrinolysis
- Date and time of ambulance departure to a hospital with hemodynamic room
- Date and time of arrival in the hospital
- Date and time of guidewire introduction (opening of the artery)

We will calculate the following time frames:

- **Patient delay**: The period between the onset of the symptoms and the call to the EMS or the FMC in a healthcare centre. The 4 pathways are included.
- **System delay**:
  - **ECG- opening of the artery:** Time between the diagnosis by ECG and the opening of the artery by PCI as the first treatment. STEMI treated with PCI after fibrinolysis will not be included in this variable. The 4 pathways are included.

- **ECG-fibrinolysis:** Time between the diagnosis by ECG and the thrombolytic administration. The 4 pathways are included.
- **Door-in Door-out (DIDO):** Time between the arrival of the patient to the FMC healthcare centre and the departure of the ambulance to a hospital with hemodynamic room. Only the 2 pathways with the FMC in a CAP or in a hospital without catheterization laboratory are included.
- **Arrival-PCI:** Time between the arrival in the hospital and the opening of the artery. Only the 3 pathways with FMC out of a hospital without catheterization are included.

Secondary variables:

The **election of treatment** will be taken from the registry as well:

- The number of patients treated only with PCI
- The number of patients treated only with Thrombolytic therapy
- The number of patients treated with both thrombolytic therapy and PCI

Mortality after diagnosis of STEMI and in the 30 days after treatment will be taken from the clinical history and assessed as dead or alive.

LVEF at discharge measured using an echocardiography and classified in 3 groups. It will be obtained from the clinical history.

- Normal >50%
- Moderately impaired 40-50%
- Severely impaired <40%

Accumulated incidence of AMI: The number of new cases of STEMI occurred in the 4 periods, which required an activation of the AMI code. The numbers will be taken from the registry *Codi IAM*.

7.3.2. Independent:

The main independent variable will be the period when the data was taken. There will be 4 periods: during and after the National lockdown, and the same periods the year before.

- The period including the *COVID-19* lockdown starting on the 12th of March and ending on the 21st of June of 2020.
- The same period of the lockdown but in 2019, starting on the 12th of March and ending on the 21st of June of 2019
- The period between the end of the *COVID-19* lockdown and the next outbreak, starting on the 22nd of June and ending on the 1st of October of 2020.
- The same period between the end of the *COVID-19* lockdown and the next outbreak but in 2019, starting on the 22nd of June and ending on the 1st of October of 2019.

7.3.3. Covariables:

The following factors will be included in the statistical analysis as they have been proved to interfere with time-to-reperfusion in a non-pandemic period. All of them will be obtained from the *Codi IAM* registry:

- **Sex** defined as Man/Female/unknown
- **Age** in years in absolute values
- **Diabetes Mellitus:** Diagnosis confirmed at the clinical history or with current treatment for diabetes. It will be assessed as diabetic or non-diabetic.
- **Distance** between the FMC and the hospital with catheterization laboratory. It is measured in kilometres and recorded by the SEM
- Antecedent of **cardiac surgery of bypass:** confirmed by the clinical history and assessed as presence or absence of the antecedent.
- **Localization** of the infarction in the final diagnosis according to the ECG and coronary angiography:
  - Anterior Q AMI
  - Inferior Q AMI
  - Lateral Q AMI
  - Posterior AMI
  - Left coronary artery
  - Non-Q AMI

- **Heart Failure** at diagnosis will be assessed by the clinical classification of Killip.
  - Killip I
  - Killip II
  - Killip III
  - Killip IV
- **Number of vessels diseased** at the coronary angiography before treatment:
  - No lesions
  - Non-significant lesion or ≤70%
  - One diseased vessel or ≥ 70%
  - Two diseased vessels or ≥ 70%
  - Three diseased vessels or ≥ 70%
- The **pathway** followed by the AMI code depending on the place the patient sought the FMC:
  - SEM (EMS)
  - CAP
  - Hospital with PCI
  - Hospital without PCI

The infection of SARS-CoV-2 will be analysed as well. It was assessed by PCR in every patient admitted in the hospital during the quarantine and the posterior period. The parameter is described as negative, meaning non-infected, and positive meaning the patient was already infected in the moment of the test. All the subjects which suffered the AMI on the periods of 2019, will be considered negative. The ones in the periods of the quarantine and posterior will be considered positive, negative, or unknown according to the PCR. The results of the PCR will be obtained from the clinical history.

8. STATISTICAL ANALYSIS:

8.1. DESCRIPTIVE ANALYSIS:

We will use different measures to analyses all the variables, including the principal ones and covariates, depending on their characteristics:

Continuous quantitative variables will be summarized by a measure of central tendency and a measure of dispersion, being mean and standard deviation if they are normally distributed or median and quartiles if they are not.

Qualitative variables will be summarized by proportions in a contingency table.

The analysis will be stratified by the covariables.

8.2. BIVARIATE ANALYSIS:

Qualitative variables will be analysed in percentages using the X^2.

Continuous quantitative variables will be analysed using the t-student.

8.3. MULTIVARIATE ANALYSIS:

Time-to-reperfusion will be compared between the 4 periods using an analysis of variance.

The accumulated incidence between the 4 periods will be compared using a Poisson regression.

Mortality will be analysed using the Cox Proportional-Hazard model.

The 3 analysis will be stratified by covariates.

9. ETHICAL AND LEGAL CONSIDERATIONS

The present protocol has been designed following the 4 ethical principles for medical research involving humans that the World Medical Association collects on the Declaration of Helsinki(44) signed in 1964 and revised for the last time in 2013. It also follows the current legislation on personal data protection:

- Regulation (EU) 2016/679 of the European parliament and of the council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation)(45).
- Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales (46).

This paper will be presented to the *Comitè Ètic d'Intervenció Clínica* from *Hospital Universitari Dr. Josep Trueta* to get the approval before developing the following study.

The main resource of data in the derived study will be the *Codi IAM* registry, where all the parameters of AMI events which required a *Codi IAM* activation have been recorded, including some personal data, as the number of clinical history. This number will help identify the patients and access the missing information which appears in the clinical history.

The informed consent was not asked before entering the patients in the registry, as it is a population registry, and all cases must be included so as to make it reliable. For this reason, we will have to take measures to protect the personal data of both sources. We will dissociate the study and pseudonymise the data. We need two different researchers, and neither of them will be part of the investigator team. One of them will take care of the research of the data, including all the subjects who suit the requirements of the sample, adding the necessary information from their clinical history and finally pseudonymising all the subjects. Then the other researcher will be able to analyse the data and obtain the results.

10. STUDY LIMITATIONS AND CHARACTERISTICS

The basic source of information in this study is a registry which has been working nearly 10 years around the Catalan territory. None or almost none of the cases will escape the registry. Thus, there is no risk of bias selection. Nevertheless, we may encounter an information bias. Even though it is an exhaustive and accurate registry, all the parameters included in the study were recorded by professionals from different services, consequently the ways in which they recollected the data may differ. They may follow different procedures, tools, and gadgets for diagnosis.

In addition, the time of the symptom's onset was obtained asking the patients. They did not probably record it, therefore, it will be approximate, which may derive in another information bias.

As it is an observational study, confounding variables may interfere in the outcomes. Some of them will be considered as covariates, but there might be factors that we have not estimated.

Silent infarction is a subtype with a difficult diagnosis, so it may be more susceptible to changes due to isolation, however, it is not recorded as silent in the *Codi IAM* registry, for this reason, it cannot be assessed in this study.

Even though the *Codi IAM* registry collects data all around Catalonia, not all the hospitals can be included in the present study, as their time-to-reperfusion cannot be compared. The delay factors affect differently each hospital, as they do not cover the same distances and they have different services and equipment, among other. Despite having the same protocol for STEMI, not all of them have the same challenge against time. For this reason, each hospital can be compared only with itself, and this study can contemplate just one of them and the results might not be exactly comparable.

11. RESEARCH TEAM AND FEASIBILITY

11.1. RESEARCH TEAM

Person in charge of data recollection: Data recollection is supposed to be performed in 160 hours. It requires access to the *Codi IAM* registry and the clinical history. This person will not be part of the investigator team.

Statistic specialist: This person will be in charge of performing the data analysis and describing the results. It has been estimated that this work will take 160 hours. This person will not be part of the investigator team.

The investigator team will be **multidisciplinary.** They will interpretate the results and set the conclusions. At least one professional of each service assisting a *Codi IAM* should constitute this team:

- Family physician representing the CAP
- Cardiologist, hemodynamic cardiologist, and EMS physician from a hospital with Catheterization room
- Cardiologist and EMS physician from a hospital without Catheterization room
- EMS physician

The **main researcher** will be one of those professionals being part of the multidisciplinary team and will write the paper once the conclusions are set.

11.2. FEASIBILITY

The access to clinical history of the patients is allowed to those clinics working on the public health system. The *Codi IAM* registry has the same requisites, but it also requires a special accreditation given to the professionals involved in the pathway. For this reason, there are 2 options: hiring someone who fulfils both requirements to be in charge of recollecting data or asking for access permission.

12. WORK PLAN AND CHRONOGRAM

12.1. WORK PLAN:

Phase: 1 Protocol design

- Activity 1: Bibliographic research was done.
- Activity 2: The present protocol was written.

Timing: This phase has already been done during a period of 8 weeks between the 14th of September and the 5th of November of 2020.

Phase 2: Clinical Research Ethics Committee

- Activity 3: The protocol will be presented at the *"Comitè Ètic d'Intervenció Clínica" (CEIC) of Hospital Dr. Josep Trueta* for the ethics approval.

Timing: This phase will take 2 months.

Phase 3: Coordination phase

- Activity 4: The principal investigator will recruit the researchers to create the research team.
- Activity 5: The principal investigator will ask for permission to access the *Codi IAM* registry and the clinical history for the person in charge of data management, just in case they did not have it.
- Activity 6: All the members of the research team will have a coordination meeting to program the chronogram on the calendar and distribute tasks.

Timing: This phase will need 1 month.

Phase 4: Data obtention

- Activity 7: The person in charge of data recollection will select all the subjects from the *Codi IAM* registry who fulfil the inclusion criteria of the present study.
- Activity 8: They will add to each profile the missing data from the clinical history.
- Activity 9: They will anonymise all the participants.

Timing: This phase will take 160hours.

Phase 5: Statistic analysis

- Activity 10: The statistic specialist will analyse the collected data and describe de results.

Timing: This phase will take 160 hours.

Phase 6: Interpretation

- Activity 11: The research team will update the bibliography.
  - This activity will be repeated once each month until the writing of the paper.
- Activity 12: The investigation team will receive and assess the results individually.
  - This activity will take 3 weeks
- Activity 13: The investigation team will discuss the results and set the conclusions.
  - They will need 2 online meetings.

Phase 7: Elaboration of the final article

- Activity 14: The principal investigator will write the paper.

Timing: This phase will need 2 months.

Phase 8: Publication of the study

- Activity 15: The article will be sent to different journals and to the services involved in *Codi IAM* to inform them about the results.

12.2. CHRONOGRAM

			2020				2021						
Phase		**Activity**	**SEP**	**OCT**	**NOV**	**DEC**	**JAN**	**FEB**	**MAR**	**APR**	**MAY**	**JUN**	**JUL**
1	**Protocol design**	1											
		2											
2	**CEIC**	3											
3	**Coordination**	4											
		5											
		6											
4	**Data obtention**	7											
		8											
		9											
5	**Analysis**	10											
6	**Interpretation**	11											
		12											
		13											
7	**Elaboration**	14											
8	**Publication**	15											

Figure 2: Chronogram

11.BUDGET

The elaboration of the protocol and the bibliography research did not require any expenses, nor will the presentation to the CEIC or the access to the data resources.

The investigator team will perform all the tasks related to coordination and interpretation of the results and they will not receive any monetary compensation.

All the meetings will be online due to the current pandemic, therefore there will not be any travel expenses.

The extraction of data from the registry and the clinical history, including the sample selection and the recollection of all the variables involved in the study will take 160 hours of work, which will cost 3500€.

The statistical analysis will take 160 hours of work, which will cost 4000€.

The payment for open access publication costs around 2000€.

Table 1: Budget

Budget	
Personal costs:	0€
External services: • **Data management 160h** • **Statistical analysis 160h**	 3500€ 4000€
Publication: • **Open access publication**	 2000€
Total:	9500€

12. CLINICAL AND HEALTHCARE IMPACT

At first, this project had the aim of getting ready for the second COVID-19 outbreak, but it has already started. Instead of losing its purpose, it has gained relevance. The need of analysing the healthcare functioning has become even clearer. Reinfection of coronavirus has been proved, meaning that we may end up going through the same circumstances again and again until a treatment or a vaccine are developed. We need to know the mistakes we made in the first National confinement in case we want to avoid or prevent them in the following ones. The present study will help determine if the lockdown had any impact on the *Codi IAM* pathways, and if it did so, which steps were affected.

Not only does this knowledge come in handy for the current pandemic, but it also might be useful in the future. According to the experts, globalization makes the spread of virus easier around the world, and just as this pandemic was expected, new ones are foreseen in the future. The current pandemic should be studied from all points of view and the medical assistance for the main diseases should be analysed in order to prevent avoidable deaths and maintain the good results of the treatments regardless of the context.

As it is mentioned before on this paper, it is not possible to study the complications of the pandemic in all the territory at once. This study will contemplate just Girona, but it would be extremely useful to adapt this investigation to the rest of the territory. It is likely that all the hospitals faced delays, but their obstacles might have been different, and they all must be identified and solved.

Finally, if the expected results were to be found, and it was proved that in a lockdown or restricted context the outcomes of ischaemic events tend to worsen, a plan should be elaborated in response. In case there was a patient delay, the response should focus on the patients. For instance, doing an awareness campaign to remind general population the importance of seeking help for ischaemic symptoms, and periodically controlling those patients with already known cardiovascular risk factors. If there was a systemic delay instead, the specific malfunctioning step should be analysed to find the causes, and then the results should be brought to the professionals involved in the AMI code through

a training. If the results were inconclusive or negative, the mentioned studies in other hospitals and other diseases must be performed anyway.

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