

# Epidemiology of sudden cardiac arrest in the western Mediterranean area based on a prospective registry

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## ABSTRACT

**Background** The epidemiology of sudden cardiac arrest (SCA) in the Mediterranean area remains unclear. The aim of this study is to determine the incidence, causes and characteristics of SCA in this setting.

**Methods** A prospective registry of out-of-hospital cardiac arrests from multiple sources of information was carried out in the Tarragona region (western Mediterranean) with a population of 610 865 inhabitants between 2014 and 2017. The attending clinician assessed the cases on-site. SCA was defined as an unexpected out-of-hospital cardiac arrest, with a presumed cardiac cause, occurring within 1 hour of symptom onset or seen in good condition within the last 24 hours. Data were obtained from the emergency medical service, forensic autopsies, hospitals and primary care centres.

**Results** A total of 639 SCAs were collected. The incidence was 34.8 (95% CI 32.2 to 37.6) cases per 100 000 person-years. The mean age was 66.9 (SD 15.6) years, and 70.1% were male. 20.5% did not receive a cardiopulmonary resuscitation (CPR) attempt. Investigations for the aetiology of cardiac arrest were conducted in hospitals in 20.3% of cases and through forensic autopsies in 36.4%. Of all SCAs with a presumed cardiac cause, 55.5% had a known cause, of which 85.3% were cardiovascular (69.8% cardiac, 15.5% cardiovascular non-cardiac and 14.6% non-cardiovascular). More cardiac causes were recorded in hospitalised patients than in forensic cases (76.9% vs 66.4%,  $p=0.042$ ). Coronary heart disease (45.6%) was the main cause, with chronic coronary heart disease (24.5%) being the most frequent type. Cases with a non-cardiac cardiovascular cause presented similar cardiovascular risk factors compared with cases with a cardiac cause. Survival was 10.2%. Chest pain prior to collapse and the use of automatic external defibrillators were associated with survival.

**Conclusion** In this western Mediterranean region, a low incidence of SCA and a low burden of coronary heart disease were found. A comprehensive, multidisciplinary approach is needed to prevent SCA.

## WHAT IS ALREADY KNOWN IN THIS TOPIC

- ⇒ The estimation of sudden cardiac arrest (SCA) incidence is primarily based on resuscitation attempt registries compiled by emergency medical services, but these do not capture all SCA cases.
- ⇒ The gold standard for studying SCA involves registries with multiple sources of information. Such registries are scarce, and none have been conducted in the Mediterranean area.
- ⇒ The incidence, causes and characteristics of SCA in the Mediterranean area remain unclear.

## WHAT THIS STUDY ADDS

- ⇒ We identified a lower incidence of SCA and a reduced coronary heart disease burden in this western Mediterranean region compared with northern Europe and North America.
- ⇒ The estimated number of SCA cases per year in Spain is 17 241, corresponding to an incidence of 37.1 per 100 000 person-years, and only one-third of SCA cases had a prior diagnosis of heart disease.
- ⇒ The assessment of SCA by the prehospital clinician achieved an acceptable positive predictive value for detecting a cardiac cause. The vast majority presented a cardiovascular cause, and both cardiac and non-cardiac cardiovascular causes shared a similar risk factor profile.

## INTRODUCTION

Sudden cardiac arrest (SCA) and sudden cardiac death (SCD) are among the leading causes of death in developed countries. It has a survival rate that barely reaches 10%, making it an unresolved public health problem.<sup>1</sup> The Mediterranean area is associated with a low incidence of cardiovascular disease due to diet and lifestyle.<sup>2</sup>

Estimation of the incidence of SCD/SCA in Europe and comparison with other regions is based on registries of resuscitation attempts compiled by emergency medical services

**HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY**

- ⇒ For the first time, a prospective registry using multiple sources of information has provided a comprehensive overview of SCA in the Mediterranean area.
- ⇒ Prospective assessment of cases in the pre-hospital phase is an easily reproducible alternative method for developing high-quality SCA registries, and the source of information on SCA causes should be considered when interpreting studies on this public health issue.
- ⇒ Although acute coronary heart disease as a cause of SCA is declining, controlling cardiovascular risk factors and using automatic external defibrillators remain effective prevention strategies.

(EMS). The incidence in the European Union was estimated at 48.6 cases per 100 000 person-years.<sup>3</sup> In the western Mediterranean area, the estimates range widely from 14.6 to 50.3 cases per 100 000 person-years.<sup>3,4</sup> Moreover, these registries do not account for SCD/SCA cases that are not attended by EMS, and most of them only keep information of survivors, thus restricting the ability to study incidence and cause of death.<sup>3,5</sup>

The definition of SCD is an out-of-hospital sudden natural death with a presumed cardiac cause that occurs within the first hour of symptom onset when witnessed or when the person appears to have been in good condition over the previous 24 hours when unwitnessed.<sup>6</sup> SCD implies a fatal event, but the term is often used interchangeably with SCA, in which both survivors and non-survivors would be included.<sup>6</sup> In autopsy-based studies, non-cardiac causes of sudden death were found for 28%–40% of cases initially labelled as SCD.<sup>7,8</sup> In a series of resuscitated out-of-hospital cardiac arrests (OHCAs) labelled as SCA, non-cardiac causes were found in 27.1% of cases.<sup>9</sup> Because of this, in the absence of a complete assessment, SCD/SCA should be considered to have a presumed cardiac origin. However, most of the global research uses SCD/SCA with a presumed cardiac cause, hampering the identification of risk markers and building preventive strategies.<sup>3</sup>

The gold standard for studying SCD/SCA involves registries with multiple sources of information; such registries are scarce, and none have been conducted in the Mediterranean area. A more accurate picture of the epidemiology and causes of SCD/SCA could be obtained by integrating multiple sources of information, such as EMS, forensic services, hospitals and primary care centres, along with a prehospital prospective assessment of each case.<sup>10</sup> The aim of this study was to better clarify the burden, causes and clinical-epidemiological characteristics of SCA/SCD in the western Mediterranean area.

**METHODS****Study design**

The Clinical and Pathological Registry of Tarragona (ReCaPTa) is a population-based registry of SCA/SCD with multiple sources of information. ReCaPTa contains data on all the OHCA attended by the EMS and all the

autopsies carried out by the reference pathology centre between April 2014 and April 2017.

**Setting**

The Camp de Tarragona region is located in the western Mediterranean in the autonomous community of Catalonia (Spain). It has an area of 2703.3 km<sup>2</sup> and 610 865 inhabitants. It is the second most important metropolitan area in Catalonia.

The EMS of Catalonia is a two-tier emergency response unit, part of the public health system, covering the entire population. In Catalonia, there is a single emergency number (112). Calls from Tarragona are coordinated through a single dispatch centre located in Reus (Tarragona). When a suspected cardiac arrest is called in, first aid help is initiated over the phone while two ambulances are dispatched: a basic life support unit with two healthcare technicians, usually arriving first to begin chest compressions and defibrillation, and an advanced life support (ALS) unit with a healthcare technician, a nurse and a physician, providing ALS according to resuscitation guidelines.

The forensic pathology centre of the Institute of Legal Medicine and Forensic Sciences of Catalonia (IMLCFC) is located in Tarragona. In the event of death, all autopsies are carried out at a single pathology centre by a specialised forensic team. In Spain, the Penal Code and the Criminal Procedure Law dictate that a forensic autopsy is required for all violent deaths and for those for which there is an unknown cause, which includes sudden and unexpected natural deaths of non-hospitalised people. The hospital network comprises three hospitals where diagnostic tests and follow-up treatments are carried out in accordance with current guidelines.<sup>11</sup>

**SCA definition and inclusion and exclusion criteria**

SCA is defined as an unexpected natural OHCA with a presumed cardiac cause that occurs within 1 hour of symptom onset if witnessed or within 24 hours of last being seen in the usual state of health if unwitnessed.

All OHCA attended or treated by EMS and all patients submitted to an autopsy at the forensic service during the 3-year study period were assessed. Cases were included if they met the definition of SCA based on the prehospital assessment made by the clinician (EMS or the forensic physician) who attended the case on location.

Cases with an obvious extracardiac cause, such as trauma, intoxication, suicide or drowning, were excluded from the initial assessment. In addition, all non-expected deaths, such as cases with terminal illness, dementia or cognitive impairment, and cases of non-residents in the study territory were excluded.

**Case assessment, registration procedure and variables**

As part of EMS, clinical assessment and treatment of patients are carried out by emergency physicians. After interviewing the witnesses and relatives of the patient, the physician is responsible for reporting the variables of the

case via an online application available on mobile devices. The epidemiological and clinical variables of prehospital care assessed in the present study were collected following the Utstein style; in addition, the type of symptoms prior to collapse and their evolution time (<1 hour, >1 hour or undetermined) were considered.<sup>12</sup>

At the forensic service, the circumstances of any death, including symptoms prior to a patient's collapse and their time of evolution, are reported on location by the forensic pathologist. The interview with the witnesses and family, the EMS report and any relevant medical history are included in a forensic prehospital assessment. An autopsy examination was carried out following the IMLCFC protocol for sudden death.<sup>13</sup> This protocol includes a complete toxicological analysis and histopathological study, as well as a genetic analysis to assess possible inherited cardiopathy in people aged <50 years without ischaemic pathology or any other cause of death.

If information was incomplete for any case, an adjudication process was carried out to determine whether it was an SCA/SCD. The causes of death are assigned following international guidelines and previous similar studies.<sup>8 14</sup> For survivors, the causes are reported in the discharge hospital diagnoses. For the unclear cases, the cause was determined by consensus among three investigators (YA, EB and AB) after a comprehensive review of emergency, hospital and forensic records. The review incorporated ECG assessments, imaging modalities when available (including echocardiography, CT and MRI), catheterisation data, laboratory analyses and the comprehensive autopsy protocol. Chronic coronary disease was defined as the presence of an inactive lesion producing  $\geq 75\%$  luminal stenosis in at least one major coronary artery, in the absence of atherosclerotic plaque disruption or thrombosis. Histological or imaging evidence of healed myocardial infarction or findings of coronary artery bypass graft were considered chronic coronary disease. Sudden arrhythmic death syndrome was defined as an unexplained sudden death occurring in an individual older than 1 year with a negative pathological and toxicological assessment.<sup>15</sup>

Cases with insufficient information to determine a cause were noted as 'indeterminate'. All reports of OHCA attended by any prehospital EMS unit were reviewed. The details of the study design and registration procedures are included in a previous publication.<sup>16</sup>

### Statistical analysis

The incidence of SCA was calculated with reference to the total population living in Camp de Tarragona in January 2015, 2016 and 2017, according to the Statistical Institute of Catalonia. This population was stratified by sex and 5-year age groups, and this same structure was applied to the entire population in Spain and other Mediterranean countries based on 2017 census data,<sup>17</sup> to obtain an estimated number of cases and an estimated incidence rate within each country. A descriptive analysis was carried out. Quantitative variables are expressed as

the mean $\pm$ SD or median and IQR. Categorical or binary values are presented as the number of cases and percentages. In the univariate analysis, the associated variable was compared with survival quantitative variables using Student's t-test if the data were normally distributed or the Mann-Whitney U test if the data were not normally distributed. Categorical or binary values were compared using the chi-squared test. A multivariable analysis was performed with survival at discharge as the dependent variable and significant prehospital variables in the univariate analysis as the independent variables. All tests were two-tailed, and  $p < 0.05$  was considered to be statistically significant. All data were analysed using the statistical package SPSS Statistics for Windows, V.19 (IBM Corp, Armonk, New York, USA). CIs for incidence rates were calculated using R software V.4.4.2 (R Foundation), with the package epiR.

### Patient and public involvement

Patients and the public have been involved in the design, selection of the results and dissemination of the results through SCD patient associations such as the Spanish Association Against Sudden Death #7, created in 2009 after the sudden death of José Duran, a young athlete who passed away playing football.

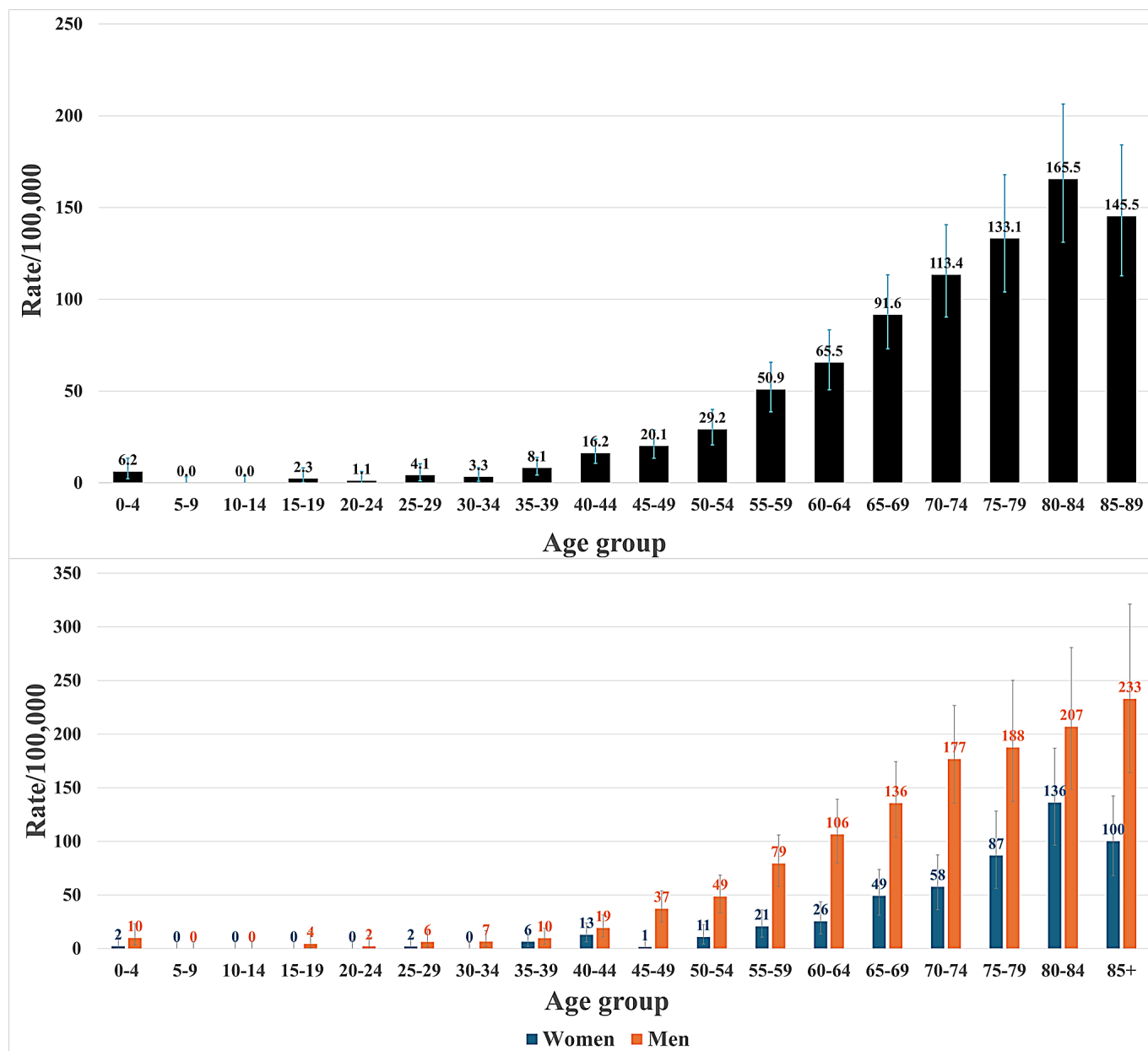
### RESULTS

Over the study period, the emergency dispatch centre received 2206 calls regarding OHCA. Online supplemental figure S1 shows the flow chart of the 639 cases that met the criteria for SCA. Among those, 565 (88.4%) cases were assessed by EMS and 74 (11.6%) by forensic services. Of the total sample, 508 (79.5%) cases received a CPR attempt, and the remaining 131 cases (20.5%) did not. Details of the EMS assessment can be found in the online supplemental figure S2. Of the 639 SCA cases, 238 (36.4%) were studied by autopsy, and hospital data were obtained for 130 cases (20.3%). The cause was established in 355 cases (55.5%). Medical history was obtained in 602 cases (94.2%).

### Incidence and clinical and epidemiological characteristics

The mean annual incidence of SCA over the 3-year study period was 34.8 cases per 100 000 person-years (95% CI 32.2 to 37.6). In men, the incidence was 48.9 per 100 000 person-years (95% CI 44.5 to 53.7) and in women, 20.7 cases per 100 000 person-years (95% CI 17.8 to 23.8). The mean age was 66.9 (SD 15.6) years, and 70.1% were male. The mean annual incidence and its 95% CI by age range and by sex are shown in figure 1.

The estimated number of SCA cases per year in Spain, based on standardisation following its population age and sex structure, is 17241 (95% CI 11683 to 25 849), corresponding to an incidence of 37.1 per 100 000 person-years (95% CI 25.1 to 55.6). The number of cases per year and the estimated incidence in other Mediterranean countries can be found in online supplemental table S1.



**Figure 1** Annual incidence and its 95% CI of sudden cardiac arrest by age range and by sex in the Camp de Tarragona, Spain (population 610 865).

The general characteristics and backgrounds of the SCA cases are given in [table 1](#). There was a history of heart disease in 219 (34.3%) SCA cases. Regarding symptoms presented prior to SCA, the most common was syncope without other previous symptoms (48.7%), followed by dyspnoea (14.6%) and chest pain (10.2%). Other less common symptoms were dizziness (4.8%), general malaise (3.3%), abdominal pain (2.2%), vomiting (2.0%), seizure (1.7%) and headache (0.5%).

#### Causes of SCA in the western Mediterranean area

The causes of SCA with a presumed cardiac origin are given in [figure 2](#). Of the 355 cases with a known cause, it was cardiac in 69.8% of cases, non-cardiac cardiovascular in 15.5% of cases, and non-cardiovascular

in 14.6% of cases. The most frequent cause was chronic coronary heart disease (24.5%), followed by acute coronary heart disease (21.1%). Coronary heart disease was the cause of 45.6% of all sudden arrest cases, 53.5% of all sudden arrest cases with a confirmed cardiovascular cause and 63.3% of all sudden arrest cases with a confirmed cardiac cause. The details of all the causes are shown in the online supplemental figure S3.

Of the 130 patients who arrived alive at the hospital, the cause of death in 13 cases was undetermined, mainly because they died before the study could be completed. More cardiac causes were collected among hospitalised patients than among those studied by the forensic service (90 (76.9%) vs 158 (66.4%),  $p=0.042$ ). Online

**Table 1** General characteristics and previous history of sudden cardiac arrest cases

| Variables                                        |             |
|--------------------------------------------------|-------------|
| <b>n</b>                                         | <b>639</b>  |
| Demographic data                                 |             |
| Male                                             | 448 (70.1)  |
| Age                                              | 66.9 (15.6) |
| Resuscitation variables                          |             |
| Resuscitation attempt                            | 508 (79.5)  |
| Witnessed cardiac arrest                         | 424 (66.4)  |
| Initial shockable rhythm*                        | 154 (27.3)  |
| Location*                                        |             |
| Home                                             | 402 (71.2)  |
| Public place                                     | 127 (22.5)  |
| Ambulance                                        | 9 (1.6)     |
| Primary care health centre                       | 27 (4.8)    |
| Symptoms prior to collapse                       |             |
| Symptoms with less than 1 hour of evolution      | 513 (80.3)  |
| Syncope without other previous symptoms          | 311 (48.7)  |
| Dyspnoea                                         | 93 (14.6)   |
| Typical chest pain or anginal equivalent         | 65 (10.2)   |
| Previous medical history                         |             |
| Medical history not obtained                     | 37 (5.8)    |
| Cardiovascular risk factors                      |             |
| Hypertension                                     | 326 (51)    |
| Diabetes mellitus                                | 169 (26.4)  |
| Dyslipidaemia                                    | 222 (34.7)  |
| Toxicology                                       |             |
| Active smokers                                   | 112 (17.5)  |
| Former smokers                                   | 87 (13.6)   |
| Alcohol abuse                                    | 110 (17.2)  |
| Illicit drug use                                 | 8 (1.2)     |
| Cardiac history                                  |             |
| Any cardiac history†                             | 219 (34.3)  |
| Myocardial infarction                            | 64 (10)     |
| Coronary heart disease                           | 92 (14.4)   |
| Congestive heart failure                         | 94 (14.7)   |
| Atrial fibrillation/atrial flutter               | 83 (13)     |
| Ventricular fibrillation/ventricular tachycardia | 8 (1.3)     |
| Implantable cardioverter defibrillator           | 3 (0.2)     |
| Permanent pacemaker                              | 18 (2.8)    |
| Other medical history                            |             |
| Chronic kidney disease                           | 60 (9.4)    |
| Seizure disorder                                 | 10 (1.6)    |
| Stroke                                           | 25 (3.9)    |
| Asthma                                           | 16 (2.5)    |
| Chronic obstructive pulmonary disease            | 88 (13.8)   |

Continued

**Table 1** Continued

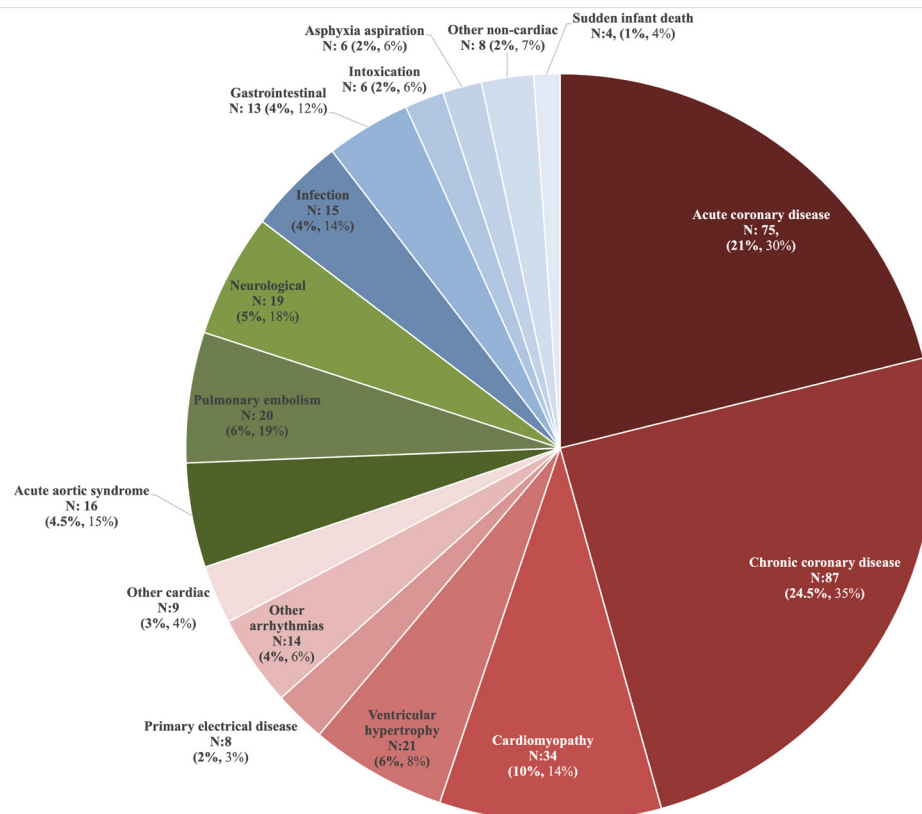
| Variables                                                                                                                                                                                                                                                                                                                                  |           |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| Obstructive sleep apnoea syndrome                                                                                                                                                                                                                                                                                                          | 17 (2.7)  |
| Pulmonary embolism                                                                                                                                                                                                                                                                                                                         | 2 (0.3)   |
| Chronic hepatopathy                                                                                                                                                                                                                                                                                                                        | 7 (1.1)   |
| Psychiatric disease‡                                                                                                                                                                                                                                                                                                                       | 66 (10.3) |
| Active malignant neoplastic disease                                                                                                                                                                                                                                                                                                        | 4 (0.6)   |
| The data are presented as the number and percentage for categorical variables and the mean and SD for quantitative variables.                                                                                                                                                                                                              |           |
| *Calculated with respect to the 565 cases attended by emergency medical services.                                                                                                                                                                                                                                                          |           |
| †Previous diagnosis of coronary heart disease, angina, myocardial infarction, congestive heart failure, cardiomyopathy, atrial fibrillation/flutter, ventricular tachycardia, supraventricular tachycardia, permanent pacemaker, implantable automatic defibrillator, severe and moderate valvular disease and congenital cardiac disease. |           |
| ‡Previous diagnosis of anxiety, bipolar disease, schizophrenia and depression.                                                                                                                                                                                                                                                             |           |

supplemental table S2 lists the causes of SCA according to whether they were reported in hospital or by forensic autopsy. Only 8% and 24.1% of patients who presented with acute and chronic coronary artery disease, respectively, had a history of previous coronary artery disease.

Of the 355 cases with known causes, in nine (2.5%) cases a pathogenic genetic alteration was found, four related to cardiomyopathies and five related to inherited arrhythmogenic syndrome. Among the 17 patients under 35 years of age who presented with SCA, an underlying cause was identified in 11 cases after the initial evaluation. Genetic testing was performed in five patients, and a genetic alteration was identified in four of them (23.5%), allowing the cause of SCA to be established in 15 of the 17 patients. The genetic test details are shown in online supplemental table S3. Among 230 autopsied cases, 70 (30.4%) had at least one positive toxicology result (see online supplemental figure S4).

### Phenotyping SCD

Prehospital case assessment by the prehospital clinician has a positive predictive value of 69.8% for detecting cardiac cause and 85.3% for detecting cardiovascular cause. The comparison of the characteristics of SCA according to the cause is shown in table 2. We noted a similar cardiovascular risk profile for cardiac and non-cardiac causes of SCA. Both types have similar figures in five out of the six cardiovascular risk factors collected, such as hypertension, dyslipidaemia, tobacco use, body mass index and abdominal perimeter. Non-cardiac cardiovascular cause has a higher rate in women and less history of heart disease. Non-cardiovascular causes involved younger patients, less frequent chest pain, more psychiatric/pulmonary disease and higher rates of positive toxicology findings compared with cardiac causes.



**Figure 2** Causes of sudden cardiac arrest with a presumed cardiac origin in the western Mediterranean Area (survivors and non-survivors). The first percentage is of the total causes of sudden cardiac arrest; the second percentage is of the total for each category (cardiac and non-cardiac causes). Among the 355 cases examined, 69.8% were due to cardiac causes (red), 15.5% to non-cardiac cardiovascular causes (green) and 14.6% to non-cardiovascular causes (blue).

In 98 CPR attempts with initial ventricular fibrillation, 36.7% were acute coronary disease, 25.5% chronic coronary disease, 13.3% cardiomyopathy, 9.2% arrhythmia, 5.1% other cardiac, 5.1% non-cardiac cardiovascular and 5.1% non-cardiovascular causes.

### Warning symptoms and factors associated with survival

Of the 508 cases that received a CPR attempt by EMS, 10.2% survived and were discharged from the hospital. Of all patients, 136 (21.3%) presented a warning symptom in the previous 4 weeks. The most frequent was syncope (13.3%), followed by dyspnoea (6.1%) and chest pain (5.7%). The results of the multivariable regression analysis model to understand the impact of different prehospital variables on survival are shown in table 3. More details about the comparison between survivors and non-survivors, as well as the univariate and multivariate analysis, are shown in online supplemental tables S4 and S5.

### DISCUSSION

Our study revealed a relatively low incidence of SCA/SCD in this region of the western Mediterranean area. Other registries in northern Europe or North America, based on multiple sources of information carried out in regions with a similar population coverage, have reported

incidences in the same range (51 and 53 cases per 100 000 person-years).<sup>18 19</sup> Incidence is best compared by age range. In this region of the western Mediterranean area, the incidence of SCA/SCD is half that reported in the Oregon Sudden Unexpected Death Study (USA) for the 55–65 and 65–74 year age ranges.<sup>19</sup> The incidence was also approximately half that reported in a study conducted in the young population of the Victoria region (Australia), which used multiple sources of information and found an incidence of 30.2 cases per 100 000 person-years for the 36–49 age range.<sup>20</sup>

A study based on four northern European OHCA registries estimated the incidence of SCD in the European Union using only data on EMS resuscitation attempts. This study projected in the European Union an annual total of 249 538 SCD cases, corresponding to an incidence of 48.6 cases per 100 000 person-years. More specifically, after adjusting the incidence for age and sex, the study estimated 23 596 cases of SCD in Spain in 2017, with an incidence of 50.3 cases per 100 000 person-years.<sup>3</sup> Using our results and applying the same methodology and population, the estimated number of SCA/SCD cases and incidence in Spain was one-third lower.

Specific factors limit comparisons with OHCA registries based solely on EMS data. By reviewing all EMS cases and

**Table 2** Comparison of the characteristics of sudden cardiac arrest with a presumed cardiac origin according to the cause

|                                                  | I (SCA with a cardiac cause) | II (SCA with a cardiovascular non-cardiac cause) | P value for the comparison between I and II | III (SCA with a non-cardiovascular cause) | P value for the comparison between I and III |
|--------------------------------------------------|------------------------------|--------------------------------------------------|---------------------------------------------|-------------------------------------------|----------------------------------------------|
| n (%)                                            | 248 (69.8)                   | 55 (15.5)                                        |                                             | 52 (14.6)                                 |                                              |
| Demographic data                                 |                              |                                                  |                                             |                                           |                                              |
| Male                                             | 197 (79.4)                   | 32 (58.2)                                        | 0.001                                       | 36 (69.2)                                 | 0.108                                        |
| Age                                              | 61.9 (14.2)                  | 59.9 (15.9)                                      | 0.403                                       | 54.5 (23.5)                               | 0.037                                        |
| Resuscitation variables                          |                              |                                                  |                                             |                                           |                                              |
| Resuscitation attempt                            | 196 (79)                     | 42 (76.4)                                        | 0.662                                       | 34 (65.4)                                 | 0.037                                        |
| Witnessed cardiac arrest                         | 155 (62.5)                   | 34 (61.8)                                        | 0.700                                       | 25 (48.1)                                 | 0.055                                        |
| Initial shockable rhythm*                        | 89/204 (43.6)                | 5/42 (11.9)                                      | <0.001                                      | 4/38 (10.5)                               | <0.001                                       |
| Location*                                        |                              |                                                  |                                             |                                           |                                              |
| Home                                             | 115 (46.4)                   | 34 (61.8)                                        | 0.009                                       | 24 (46.2)                                 | 0.837                                        |
| Public place                                     | 76 (30.6)                    | 8 (14.5)                                         | 0.042                                       | 4 (7.7)                                   | 0.002                                        |
| Ambulance                                        | 6 (2.4)                      | 0 (0)                                            | 0.296                                       | 1 (1.9)                                   | 0.311                                        |
| Health centre                                    | 7 (2.8)                      | 0 (0)                                            | 0.328                                       | 9 (17.3)                                  | <0.001                                       |
| Survival to hospital discharge†                  | 45 (18.1)                    | 2 (3.6)                                          | 0.006                                       | 4 (7.7)                                   | 0.066                                        |
| Symptoms prior to collapse                       |                              |                                                  |                                             |                                           |                                              |
| Symptoms with less than 1 hour of evolution      | 194 (78.2)                   | 41 (74.5)                                        | 0.554                                       | 36 (69.2)                                 | 0.163                                        |
| Syncope                                          | 123 (49.6)                   | 22 (40)                                          | 0.199                                       | 19 (36.5)                                 | 0.889                                        |
| Dyspnoea                                         | 22 (8.9)                     | 4 (7.3)                                          | 0.809                                       | 11 (21.2)                                 | 0.003                                        |
| Typical chest pain or anginal equivalent         | 33 (13.3)                    | 4 (7.3)                                          | 0.348                                       | 0 (0.0)                                   | 0.004                                        |
| Previous medical history                         |                              |                                                  |                                             |                                           |                                              |
| Cardiovascular risk factors                      |                              |                                                  |                                             |                                           |                                              |
| Hypertension                                     | 113 (45.6)                   | 18 (32.7)                                        | 0.163                                       | 11 (21.2)                                 | 0.003                                        |
| Diabetes mellitus                                | 58 (23.4)                    | 5 (9.1)                                          | 0.043                                       | 9 (17.3)                                  | 0.616                                        |
| Dyslipidaemia                                    | 86 (34.7)                    | 15 (27.3)                                        | 0.387                                       | 11 (21.2)                                 | 0.147                                        |
| Toxicology                                       |                              |                                                  |                                             |                                           |                                              |
| Active smokers                                   | 61 (24.6)                    | 14 (25.5)                                        | 0.353                                       | 12 (23.1)                                 | 0.949                                        |
| Former smokers                                   | 36 (14.5)                    | 1 (1.8)                                          | 0.008                                       | 5 (9.5)                                   | 0.471                                        |
| Alcohol abuse                                    | 44 (17.7)                    | 9 (16.4)                                         | 0.327                                       | 10 (19.2)                                 | 0.853                                        |
| Illicit drug use                                 | 4 (1.6)                      | 2 (3.6)                                          | 0.643                                       | 2 (3.8)                                   | 0.524                                        |
| Cardiac history                                  |                              |                                                  |                                             |                                           |                                              |
| Any cardiac history‡                             | 71 (28.6)                    | 3 (5.5)                                          | 0.001                                       | 12 (23.1)                                 | 0.709                                        |
| Myocardial infarction                            | 25 (10.1)                    | 1 (1.8)                                          | 0.045                                       | 0 (0)                                     | 0.031                                        |
| Coronary heart disease                           | 30 (12.1)                    | 0 (0)                                            | 0.016                                       | 3 (5.8)                                   | 0.412                                        |
| Congestive heart failure                         | 23 (9.3)                     | 1 (1.8)                                          | 0.103                                       | 5 (9.6)                                   | 0.888                                        |
| Atrial fibrillation/atrial flutter               | 24 (9.7)                     | 0 (0)                                            | 0.021                                       | 7 (13.5)                                  | 0.614                                        |
| Ventricular fibrillation/ventricular tachycardia | 3 (1.2)                      | 0 (0)                                            | 0.200                                       | 0 (0)                                     | 0.658                                        |
| Implantable cardioverter defibrillator           | 3 (1.2)                      | 0 (0)                                            | 0.303                                       | 0 (0)                                     | 0.725                                        |
| Permanent pacemaker                              | 6 (2.4)                      | 0 (0)                                            | 0.148                                       | 0 (0)                                     | 0.481                                        |
| Other medical history                            |                              |                                                  |                                             |                                           |                                              |
| Chronic kidney disease                           | 14 (5.6)                     | 0 (0)                                            | 0.064                                       | 3 (5.8)                                   | 0.986                                        |

Continued

Table 2 Continued

|                                           | I (SCA with a cardiac cause) | II (SCA with a cardiovascular non-cardiac cause) | P value for the comparison between I and II | III (SCA with a non-cardiovascular cause) | P value for the comparison between I and III |
|-------------------------------------------|------------------------------|--------------------------------------------------|---------------------------------------------|-------------------------------------------|----------------------------------------------|
| Seizure disorder                          | 4 (1.6)                      | 2 (3.6)                                          | 0.155                                       | 2 (3.8)                                   | 0.578                                        |
| Stroke                                    | 5 (2.0)                      | 1 (1.8)                                          | 0.269                                       | 0 (0)                                     | 0.383                                        |
| Asthma                                    | 2 (0.8)                      | 3 (5.5)                                          | 0.049                                       | 3 (5.8)                                   | 0.029                                        |
| Chronic obstructive pulmonary disease     | 25 (10.1)                    | 7 (12.7)                                         | 0.202                                       | 13 (25)                                   | 0.023                                        |
| Obstructive sleep apnoea syndrome         | 9 (3.6)                      | 2 (3.6)                                          | 0.267                                       | 3 (5.8)                                   | 0.791                                        |
| Pulmonary embolism                        | 0 (0)                        | 1 (1.8)                                          | 0.079                                       | 0 (0)                                     | 1                                            |
| Chronic hepatopathy                       | 4 (1.6)                      | 1 (1.8)                                          | 0.506                                       | 2 (3.8)                                   | 0.606                                        |
| Psychiatric disease§                      | 29 (11.7)                    | 11 (20)                                          | 0.094                                       | 13 (25)                                   | 0.041                                        |
| Active malignant neoplastic disease       | 0 (0)                        | 1 (1.8)                                          | 0.079                                       | 1 (1.9)                                   | 0.091                                        |
| Autopsy data¶                             |                              |                                                  |                                             |                                           |                                              |
| Body mass index                           | 30.9 (5.6)                   | 30.3 (7.1)                                       | 0.394                                       | 28.4 (7.4)                                | 0.017                                        |
| Heart weight                              | 546.5 (140.6)                | 447.1 (139.1)                                    | 0.004                                       | 403.2 (97.5)                              | <0.001                                       |
| Abdominal perimeter (cm)                  | 104.9 (13.8)                 | 101.4 (13.7)                                     | 0.297                                       | 97.1 (17)                                 | 0.034                                        |
| Intraventricular septal wall (mm)         | 16.4 (3.4)                   | 17.0 (4.6)                                       | 0.638                                       | 13.9 (3.8)                                | 0.007                                        |
| Posterior wall of the left ventricle (mm) | 16.4 (3.6)                   | 16.2 (4.3)                                       | 0.848                                       | 14.9 (3.7)                                | 0.121                                        |
| Any positive toxicology test**            | 41 (26.2)                    | 10 (27.8)                                        | 1                                           | 19 (50%)                                  | 0.008                                        |

The data are presented as the number and percentage for categorical variables and mean and SD for quantitative variables.

\*Calculated with respect to the 565 cases attended by emergency medical services.

†Calculated with respect to the 508 resuscitation attempts.

‡Previous diagnosis of coronary heart disease, angina, myocardial infarction, congestive heart failure, cardiomyopathy, atrial fibrillation/flutter, ventricular tachycardia, permanent pacemaker, implantable cardioverter defibrillator, severe and moderate valvular disease and congenital cardiac disease.

§Previous diagnosis of anxiety, bipolar disease, schizophrenia or depression.

¶Cases >18 years of age with an autopsy.

\*\*Calculation based on the 230 cases with available toxicology test results.

SCA, sudden cardiac arrest.

autopsies, we likely captured most SCA/SCDs. This quality control can minimise under-reporting of EMS cases by as much as 25%.<sup>21</sup> Second, the high EMS coverage has reduced resuscitation attempts handled solely by primary care.<sup>4</sup> Third, in the few cases not attended by the EMS ALS physician, the assessment was done by primary care physicians, referring SCD cases for autopsy. In this study, 20.5% of patients with SCA/SCD had no resuscitation attempt, and 11% came from the forensics service. This approach allowed a broader analysis of SCA/SCD beyond EMS resuscitation attempts cases, revealing the weight of each source of information.

We identified the cause of SCA in 55.5% of cases, the highest rate reported, to the best of our knowledge, in a registry with multiple sources of information covering the general population. In patients under 50 years of age, the cause of SCA was identified in 91.8% of cases, a percentage similar to that reported in another registry focused on a young population conducted in

Australia and higher than that of a registry conducted in Denmark.<sup>20 22</sup> Our study uniquely compared forensic and hospital SCA/SCD causes, revealing more cardiac cases in hospitalised patients. This is the first study enabling such a comparison, helping the interpretation of similar research. In the present study, 36% of the causes were reported by the forensic service, compared with only 12% in a similar cohort.<sup>19</sup> In our sample, only one-third of SCD cases had a history of heart disease, compared with 15% in a previous western Mediterranean study.<sup>23</sup>

Based on the literature, coronary heart disease is responsible for 70%–80% of SCDs when only cardiac causes are considered, with acute coronary heart disease being the main cause.<sup>10 24</sup> In our study, 45% SCA/SCD with a presumed cardiac cause and 63% SCA/SCD with a confirmed cardiac cause were due to coronary heart disease, followed by cardiomyopathy and ventricular hypertrophy. Similar findings in the POSTSCD study confirm the rise in non-ischaemic SCA/SCD

**Table 3** Results of the multivariable regression analysis of prehospital variables associated with survival at hospital discharge

|                                                                        | OR        | 95% CI |       | P value |
|------------------------------------------------------------------------|-----------|--------|-------|---------|
|                                                                        |           | Lower  | Upper |         |
| Demographics                                                           |           |        |       |         |
| Age                                                                    |           |        |       |         |
| Location                                                               | 0.97      | 0.95   | 0.99  | 0.006   |
| Home                                                                   | Reference |        |       |         |
| Public place                                                           | 3.70      | 1.76   | 7.77  | 0.001   |
| Ambulance                                                              | 8.12      | 1.24   | 53.30 | 0.029   |
| Health centre                                                          | 5.58      | 1.53   | 20.37 | 0.009   |
| Resuscitation variables                                                |           |        |       |         |
| Automatic external defibrillator use prior to emergency medical system | 2.99      | 1.12   | 7.97  | 0.028   |
| Initial shockable rhythm                                               | 8.47      | 3.62   | 19.6  | <0.001  |
| Symptoms prior to collapse                                             |           |        |       |         |
| Chest pain                                                             | 2.44      | 1.04   | 5.71  | 0.040   |

causes.<sup>8 9</sup> Chronic coronary heart disease is the leading cause, followed by acute coronary heart disease. This may be due to an ageing population, improved acute myocardial infarction treatment and better symptom timing assessment before collapse.

Knowledge of SCA/SCD phenotyping is essential to build accurate predictive models and targeting strategies.<sup>25</sup> The proportion of cardiovascular risk factors in the present study is similar to previous studies.<sup>8 9</sup> Non-cardiac cardiovascular sudden death shares similar risk factors with cardiac sudden death, suggesting common preventive strategies such as risk factor control and healthy lifestyle promotion. By contrast, non-cardiovascular sudden death appears to diverge from a cardiac profile.

Regarding familial heart disease, the proportion of inherited cardiomyopathies and primary electrical diseases found in the present study is similar to another series.<sup>26</sup> Our findings suggest that systematically reporting symptoms before collapse could improve SCA/SCD phenotyping. A more complex SCA/SCD case assessment and adjudication system, based on expert committees, found lower positive predictive values for detecting cardiac or arrhythmic causes.<sup>7 8</sup>

Survival was poor and linked to factors such as pre-collapse chest pain or automatic external defibrillator use prior to the arrival of EMS, as it was described previously.<sup>27</sup> A campaign performed in Australia, raising awareness that chest pain is a symptom of a heart attack, has helped reduce OHCA incidence.<sup>28</sup> Our findings underline the need for short-term prevention strategies

aiming to prevent SCA/SCD within the minutes, hours and days before the event.<sup>29</sup>

Our study has some limitations. We did not consult death certificates. Regarding a history of heart failure, the ejection fraction was not specified.

## CONCLUSIONS

We identified a lower incidence of SCA/SCD and burden of coronary heart disease in this western Mediterranean region compared with northern Europe and North America. The vast majority of SCA/SCDs with a presumed cardiac origin were secondary to a cardiovascular cause. Survival has been associated with prior symptoms and initial care. A multidisciplinary approach is needed to reduce the burden of SCD.

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