Antemortem characterization of sudden deaths as first-manifestation in Italy

Ante-mortem characterization of sudden deaths as first-manifestation in Italy.

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Abstract

Purpose. There is a relative paucity of data on ante-mortem clinical characteristics of young (age 1 to 35 years) sudden death (SD) victims. Aim of the study was to characterize ante-mortem characteristics of SD victims, in a selected national cohort identified by web search.

Methods. A dataset of all SD, between January 2010 and December 2015 was built from the national forensic and medical records, integrated with Google™ search module. Families were contacted to obtain consent for interviews. Data were obtained on ante-mortem symptoms. ECG and autopsy data were collected where available.

Results. Out of 301 SD cases collected, medical and family history was available in 132 (43.9%) patients. Twenty-eight (21.1%) had a positive family history for SD. SD occurred during sport/effort in 76 (57.6%). One hundred and twelve (85%) SD cases had no prior symptoms. Autopsy data was available in 100 out of 132 (75,8%) cases: extra cardiac cause was identified in 20 (20%). Amongst the 61 cases with a cardiac diagnosis, 21 (34%) had hypertrophic cardiomyopathy. Among the 19 (19%) victims without no structural abnormalities, molecular autopsy identified pathogenic variants for channelopathies in 9 cases. Ten (10%) victims had no identifiable cause.

Conclusions. Most SD were due to cardiac causes and occurred in previously asymptomatic patients, mainly during strenuous activity. In a minority of cases, no cause was identified. The web-based selection criteria, and incomplete data retrieval, need to be carefully taken into account for data interpretation and reproducibility.

Introduction

Sudden death (SD) is a significant public health concern, particularly devastating in young patients. In cohorts of subjects aged 1 to 40 years, the incidence of SD has been reported in the range of 0.9 to 8.5 per 100,000 person-years,[1–3] with cardiac disease accounting for the vast majority of non-traumatic cases.[4–7]

Sudden arrhythmic death occurs more commonly at rest or during sleep and up to 90% of the victims do not present prior symptoms or identifiable risk factors for Sudden Arrhythmic Death Syndrome (SADS).[8] An autopsy-based series of a US military population (18 years of age and over) undergoing active surveillance, however, reported that 68.4% of SD were witnessed; within the latter, 40% were temporally associated with exertion, and a prodrome was documented within one week from the terminal event in half of the victims.[9] Therefore, despite being, by definition, unexpected and rapid, SD may be seen, from a temporal perspective, as a sequence of events that may manifest weeks before the terminal event.

Due to the lack of data on ante-mortem characteristics of young SD victims, our study aimed to analyze the ante-mortem characteristics of SD as the first manifestation in young adults (<35 years old) in a nationwide population-based analysis study.

Methods

Patient cohort. A dataset of young SD victims (age 1 to 35 years) who suffered SD as a first clinical manifestation, between January 1st 2010 and December 31st 2015, was created. In the absence of a national registry on sudden death, the dataset was built based on the national forensic and medical records, integrated by Google™ search module (thirty-one Italian search items were used, see full details in the *Supplemental table X*).

SD was defined as follows: non-traumatic, unexpected fatal event occurring within one hour from the onset of symptoms in a healthy subject (if death was not witnessed, the definition applies when the victim was in good health 24 hours before the event).

Inclusion criteria were the absence of known disease (cardiac or extracardiac), and positive toxicology screening (**Figure 1**). Of the total 412 SD victims identified, after careful review by two independent researchers (A.F. and M.A.), 111 did not satisfy inclusion criteria (see details in *Supplemental figure* 1).

SD was defined as unexplained when no cause was identified after a complete and comprehensive autopsy examination, including histologic and toxicological studies.

Data collection. The investigators contacted the local hospitals where the SD was registered. Family members and/or 1st-degree relatives of the SD victim were offered participation to the study and contacted by the investigators to obtain formal consent for interviews. A standardized questionnaire which focused on ante-mortem, as well as post-mortem (autopsy and genetic tests) data, was used (details int the Supplemental data). The questionnaire specifically focused on: 1) SD prodromes, 2) past medical history, including congenital abnormalities and abnormal anthropometric measurements, 3) detailed breakdown of the sports participation, 4) first assistance given to the victim (e.g. cardio-pulmonary resuscitation), presence of on-site medical personnel, Basic Life Support and early defibrillation with an automatic external defibrillator (BLSD), proficiency among rescuers, AED availability, first recorded rhythm at AED arrival, number of shocks. Where available, ECG and autopsy data were collected from the relatives, as well as from forensic and medical records and sport medicine physicians distributed along the Italian territory. Each case was carefully investigated, and available witnesses were interviewed personally by the investigators. Additionally, primary data was retrieved via the EMS run sheets. Any missing data prevented the enrollment of the patient in the study. Autopsies were performed at the

respective centres according to Italian pathologists guidelines, recommending collection of histological and toxicological data (including a panel of most common abuse substances and alcohol). The study protocol was approved by the local ethics committee at the "Città della Salute e della Scienza di Torino" Hospital and Bordeaux.

Statistics. Continuous variables were expressed as mean +/- standard deviation (SD) and categorical variables as number and percentage. A t-test or a Chi-square test was performed for comparison of continuous and categorical variables, respectively. P values < 0.05 were considered statistically significant. Data were analyzed using SPSS software 20.

Patient and public involvement. This research was performed with the participation of the victims' relatives, who represented the largest source of ante-mortem data of the victims. Relatives were not invited to comment on the study design or interpret the results.

Results

Study population. During the study period (from 2010 through 2015), Italy had a mean population of 60.2 million residents, of whom 21.1 million were in the age group 1 to 35 years.[10] The number of deaths in this age group and period was 7304.

In the present study we identified 301 cases of SD, yielding an estimated annual incidence of sudden unexpected death in Italy of 0.24 cases per 100,000 persons (95% confidence interval, 0.13 to 0.45). Males had a higher incidence of SD (0.4 vs. 0.1 cases per 100,000 persons, $P < 0.001$).

Majority of the victims were males (81%) and SD occurred at a mean age of 22±7.9 years (**Figure 2**). 28 / 132 (21.1%) cases had a family history of SD (first-degree relatives in 9% of

cases; second/third degree relatives in 12.1%). 101 / 132 (76.5%) practiced sport; 67 of which (50.8%) at high-level (**Table 1**)

Age, mean (± SD), years	***22 ± 7.9***
Male, n (%)	*107 (81%)*
Ethnicity, n (%)	
Caucasian	*126 (95.4%)*
African	*4 (3.0%)*
Hispanic	*1 (0.8%)*
Asiatic	*1 (0.8%)*
BMI, mean (± SD)	*24 ± 6.5*
Distinctive features, n (%)	
Multiple nevi	*5 (3.8%)*
Marfanoid habitus	*3 (2.3%)*
Pectus excavatum	*1 (0.8%)*
Pectus carinatum	*1 (0.8%)*
Region, n (%)	
North	*35 (26.6%)*
Centre	*46 (34.8%)*
South	*51 (38.6%)*
Occupational Status, n (%)	
Student	*64 (48.5%)*
Employee	*17 (12.9%)*
Athlete	*8 (6.0%)*
Other	*43 (32.6%)*

Sport activity, n (%)	
Active (>5 hr/wk)	*43 (32.6%)*
Amateur	*34 (25.8%)*
None	*31 (23.5%)*
Competitive	*24 (18.2%)*

Table 1. Demographic characteristics of the sudden death cohort

Ante-mortem characteristics. 112/132 (84.8%) victims had no prior symptoms, 13 (9.8%) reported intense fatigue in the 2 weeks preceding the SD event, 3 (2.3%) suffered from palpitations in the last 3 months, 2 (1.5%) had a history of syncope, and 2 (1.5%) of pre-syncope. Ten SD victims (7.6%) were on antibiotic therapy at the time of death ~~(penicillin n=4; fluoroquinolones n=3; macrolides n=2; sulfonamides n=1).~~ Fourteen (10.6%) victims had associated pyrexia on the day or days before the event (**Table 2**). One victim, a male professional bodybuilder, reported regular use of anabolic steroids; post-mortem examination revealed a previously undiagnosed hypertrophic cardiomyopathy (with a heart weight of 780 g). 4 victims~~, all male,~~ reported use of protein powder; of these, 2 did not undergo post-mortem examination, 1 had a final diagnosis of HCM and 1 of a ruptured cerebral aneurysm (**Table 2**).

Symptoms before SD, n (%)	
No prior symptoms	112 (84.8%)
Fatigue	13 (9.8%)
Palpitations	3 (2.3%)
Syncope	2 (1.5%)
Pre-syncope	2 (1.5%)
Allergies, n (%)	9 (6.8%)
Pulmonary disease, n (%)	
History of pneumonia	8 (6%)
Asthma	3 (2%)
Tuberculosis	1 (0.8%)
Previous surgery, n (%)	19 (14.4%)

History of seizures, n (%)	3 (2.3%)
Associated pyrexia, n (%)	14 (10.6%)
Recent trauma, n (%)	5 (3.8%)
Medical therapy at the time of SD, n (%)	
NSAID	4 (3%)
Antibiotics	10 (7.6%)
Oral Contraceptives	3 (12%)†
Corticosteroids	2 (1.5%)
Insulin	1 (1%)
Anti-epileptic drugs	1 (1%)
No therapy	111 (84.1%)
Cardiovascular Risk factors, n (%)	
Smoke	10 (7.6%)
Hypertension	0
Type 1 Diabetes Mellitus	2 (1.5%)
Drugs addiction, n (%)	5 (3.8%)
Energy drinks routine use, n (%)	12 (9.1%)
Anabolic steroids, n (%)	1 (1%)
Protein Powder, n (%)	4 (3%)
Sudden increase in size in the last 3 months (when applicable), n (%)	5 (3.7%)‡
†among female victims ‡ among victims < 20 years of age	

Table 2. Clinical and behavioural variables of the sudden death victims

Circumstances of death. A significantly higher number of SD events occurred in the winter months (p=0.1, **Table 3**). In 116/132 (87.9%), the SD event occurred in an urban setting. 78 (57.6%) of SD events occurred in the context of high adrenergic tone (sport n=37, physical effort n=31; immediate post-effort recovery n=10). In 5 cases (3.8%), SD took place during intense emotional stress. ~~In 30 (22.2%) cases SD occurred at rest and in 12 (8.9%) while sleeping. 101 (76.5%) of SD events were witnessed (in sporting facilities n= 45; at home n= 20; at school n = 12; other settings n= 24).~~

Time, n (%)	
Morning (6am – 12pm)	***32 (24.2%)***
Afternoon/evening (12pm – 11pm)	***71 (53.8%)***
Night (11pm – 6am)	***33 (25%)***
Season, n (%)	
Winter	*42 (31.8%)*
Spring	*33 (25%)*
Summer	*27 (20.5%)*
Autumn	*30 (22.7%)*
Location, n (%)	
Urban	*116 (87.9%)*
Rural	*16 (12.1%)*
Witnessed, n (%)	101 (76.5%)
SD occurred during, n (%)	
Sport/ Effort/ Post-effort recovery	76 (57.6%)
Rest/ Sleep	42 (31.8%)
Emotional stress	5 (3.8%)
Miscellanea	9 (6.8%)
Unknown	
SD took place at	
Sport facility	49 (37.1%)
Home	43 (32.6%)
School	12 (9.1%)
Other (i.e. public streets, bars, beaches etc.)	28 (21.2%)

Table 3. *Circumstances of sudden death*

Resuscitation data. Amongst the 101 witnessed SD events, CPR began promptly (within 1 minute) in 28 cases (27.7%). Overall, 120/132 (91%) SD cases received CPR. An Automatic External Defibrillator (AED) was available onsite in 19 cases (14.4%). 45 of 120 rescuers (37.5%) were BLS-certified. ~~41 (31%) victims presented with gasping, and 31 (23.5%) had their eyes wide open with a fixed gaze.~~ The first recorded rhythm obtained by AED analysis at arrival was available in 101 victims (56 [55.4%] VF; 39 [38.6%] asystole; 6 [6%] pulseless

electrical activity). ~~55/ 132 (41.7%) victims received at least one shock.~~ Complete data on the immediate management by bystanders and emergency medical personnel are included in **Table 4**.

Behaviour of the victim, n (%)	
Gasping	41 (31%)
Eyes wide open	31 (23.5%)
Seizure-like movements	28 (21.2%)
Urine/stool emission	24 (18.2%)
Vomit	13 (9.8%)
AED available onsite, n (%)	19 (14.4%)
AED onsite (only sports centers, n= 49)	7 (14.3%)
CPR began promptly (within 1 minute), n (% out of witnessed SD)	28 (27.7%)
CPR performed by BLS certified bystander, n (% out of total nr of CPRs)	45 (37.5%)
Ventilation performed, n (%)	30 (22,7%)
Rhythm at AED arrival, n (% among available tracings, n= 101)	
VF	56 (55.4%)
ASY	39 (38.6%)
PEA	6 (6%)
Shocked at least once, n (%)	55 (41,7%)

Table 4. Resuscitation data

Electrocardiographic data. ECGs were available in 45/ ~~out of~~ 132 (34%) subjects, and in 8% of the cases it was performed as routine preparticipation sports screening. 4 presented incomplete right bundle block, 9 had early repolarization, 1 short QT interval, 1 long QT interval. ~~Mean PR interval was 171 ± 14 ms. Mean QRS duration was 93 ± 11 ms.~~ The patient with a short QT interval had 289 ms (***Figure 3, supplementary material***). The patient with long QT interval had 540 ms and was undertaking an antibiotic therapy (penicillin). The site of early repolarization was inferior with horizontal slope in all cases.

Post-mortem characteristics. Autopsy data were available in 100 cases. Cardiac structural disease accounted for 61 (61%) of all autopsied SD events. Extracardiac causes were identified

in 20 cases (20%). There were no identified structural abnormalities in 19 (19%) of the available autopsies (**Figure 4-A**). Among the sudden cardiac deaths, 21/ ~~out of~~ 61 (34.4%) documented Hypertrophic Cardiomyopathy (HCM), 16 (26.2%) Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC), 14 (23%) Ischemic Heart Disease (IHD), 7 (11.5%) Myocarditis, 2 Aortic Dissection (3.3%), and 1 (1.6%) an anomalous origin of the coronary arteries (**Figure 4-B**). Extracardiac causes of SD included cerebrovascular events (n=15, 75% among extracardiac SD), possible drowning (n=1), sepsis (n=1), and aortic dissection (n=3). Among the 61 cases presenting structural cardiac disease, the final diagnosis was achieved by gross and histopathologic studies, without genetic testing. Among the 19 victims without signs of macroscopic or microscopic cardiac structural disease, genetic testing for variants implicated in heritable cardiomyopathies and/or channelopathies (long QT syndrome, short QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia) was performed as per consensus guidelines. In the aforementioned 19 cases, a final molecular diagnosis of Brugada Syndrome (BrS) was reached in 3, Long QT Syndrome (LQTS) in 5 patients, and Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) in 1 patient. The cause of death was not identified in 10 cases (Sudden Unexplained Death).

The cause of death varied according to age group; considering the four most common causes of SCD, HCM and myocarditis were the most frequent causes of SD in the 16 to 20 age group, ARVC was the most frequent cause of SD in the 26 to 30 age group. The incidence of IHD as a cause of SD increased progressively from the ages of 21 to 35, with no reported incidences in the 16 to 20-year age group (**Figure 5**).

Clinical screening among relatives of the victims. Screening data among relatives (parents and siblings) was available in 70 SD cases. In each of these, at least an ECG or echocardiogram was performed. Genetic testing was performed in only 5 cases. A definite clinical diagnosis

was established in 6 of the 70 (8.5%) screened families (CPVT, n=1; BrS, n=1; ARVC, n=2; HCM, n=1). There was one diagnosis of aortic stenosis in the mother of a victim. No deaths occurred amongst relatives of the victims over 41 ±11 months following the index event in the proband.

Discussion

In the present study, based on a national cohort identified by web search, we report ante-mortem and post-mortem data from a selection of SD cases aged 1 – 35 years. The findings are as follows: 1) Only 15% of subjects had symptoms before the SD event, with fatigue, palpitations, syncope and pre-syncope being the most commonly reported symptoms from patient relatives. 2) Close to two-thirds of SD events occurred in the context of high adrenergic tone. 3) The age-related distribution of SD showed a bimodal trend, with the first peak at 15-20 years and a second peak at 30-35, with the underlying causes differing significantly between age groups.

The estimated annual incidence of sudden unexpected death in Italy in the study period was 0.24. However, a recent nationwide study[11] has reported estimates up to ~1.3/100,000-person-years. Web-based population selection, together with difficulties in complete data retrieval, therefore need to be carefully considered for data interpretation and reproducibility. However, given the paucity of data on ante-mortem clinical characteristics of young SD victims, in our opinion, the present study provides interesting insights on the terminal event leading to SD, in which, despite an attempted resuscitation in almost every victim, there was not, in any cases and at any moment, a return of spontaneous circulation (ROSC).

The majority of SD events in the present study were associated with high adrenergic tone-related activities. These findings contrast with the results of Bagnall et al. [11], where most of

the deaths occurred at rest or during sleep. There are several potential explanations for this discrepancy. In our study, the leading causes of SD were ARVC, HCM and IHD, conditions that have a strong correlation with physical exercise-induced SD. The most frequent causes of death in the study by Bagnall et al., instead, were Sudden Unexplained Cardiac Death (with an overall diagnostic yield of genetic testing of 27%, mostly for channelopathies), CAD and DCM. The presumably higher rate of primary arrhythmic syndromes may then account for the higher rate of parasympathetic and non-stress-related adrenergic circumstances of death. Another potential explanation is population selection bias, with SD events occurring in the context of sporting activity being more likely to be covered by media and therefore identified by the Google search™ module. In this respect, the abovementioned study by Bagnall and colleagues, in which all cases of sudden death in subjects 1 to 35 years of age were prospectively collected by forensic pathology centers, probably represents a more accurate and representative data.

Concerning acute management of SD events, even though the majority of SD events were witnessed, less than a third received immediate CPR (defined as CPR delivery within 1 minute). Furthermore, only a minority of resuscitation providers were BLS trained, and AEDs were available in an even smaller proportion of cases.

These findings further underscore the importance of BLS-D training promotions and campaigns for more widespread availability of AED to improve the outcome of resuscitation.

SD was associated with a bimodal trend in the present study, with the first peak at 15-20 and a second peak at 30-35 years of age. The underlying causes are significantly different between age groups, with myocarditis and HCM representing the most common findings in the first age group, and IHD and HCM accounting for more than half of SCD in the latter. The most common finding at autopsy was a cardiac structural abnormality, followed by an extracardiac

structural pathology. However, a fifth of the cases had no evidence of structural anomalies. Genetic analysis carried out on the latter group reached a diagnostic yield of 47%. Therefore, autopsy combined with molecular analysis was associated with a substantially higher likelihood of determining the cause of SD. Acknowledging the potential for misclassification of abuse substances overdose sudden deaths as cardiac in the absence of a toxicology screening at autopsy, as reported by two recent large reports[12,13], in Italy, in cases of SDs, the Public Prosecutor commonly reqests complete forensic investigation, including the collection of toxicological data. Accordingly, in our Country no particular risks about this misclassification exist.

Clinical perspectives

It is still controversial whether mass screening programs hold a favorable cost-effectiveness to prevent SD among children and young adults. However, our study shows that a significant proportion of victims had a positive family history for SD, thus suggesting the importance of a targeted and thorough cardiological and genetic examination among first and second–degree relatives by a multidisciplinary team. Since approximately 40% of SCD in the young remain unexplained after the autopsy and given the genetic basis of most underlying cardiovascular causes, a specific screening should always be preceded by a complete and accurate autopsy alongside DNA storage of the victim. In this setting, autopsy plays an essential role, and should be performed in any case of SD in the young, always associated to genetic testing, not only in unexplained cases but also in the structurally abnormal hearts, in search of genotype-phenotype associations. Standard molecular autopsy panels will typically include the four main genes accounting for a significant number of previously unexplained SCDs, including *KCNQ1* (LQT1), *KCNH2* (LQT2), *SCN5A* (LQT3/BrS1), and *RYR2* (CPVT1).

Finally, the results of our investigation call for further AED diffusion and BLS-D training campaigns among the general population.

Limitations

The present study has several limitations. The authors acknowledge the fact that the dataset is not based on a prospective national registry, and that poorer and minority populations not covered by the media might have been excluded. We also acknowledge that only 132 of 301 SD cases were included for analysis. Thus a large majority of cases were not thoroughly examined and the cohort analyzed may substantially be biased relative to the (unknown) young SD population in Italy during the study period. Secondly, autopsies and genetic testing, when performed, were carried out at different Institutions throughout the Country, with significant methodological differences and accuracy. Lastly, this was not a geographically or ethnically diverse population, and the results might not apply to other geographic regions and other populations.

Conclusions

The majority of sudden unexpected deaths in patients under 35 years are due to cardiac causes. Cardiomyopathies prevail in younger age, while ischemic heart diseases in the older. The vast majority of the SD occur in previously asymptomatic patients, mainly during strenuous activity, further highlighting the importance of screening programs. In 10% of the cases no clear cause of SD could be identified. Web-based population selection, together with difficulties in complete data retrieval, need to be carefully considered for data interpretation and reproducibility.

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Conflicts of interest: none

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Contributorship statements

Dr Frontera, Dr Anselmino, Dr Matta, Dr Aschieri, Dr Castelli, Dr Gaita, Dr Notarstefano, Dr Haissaguerre, Dr Baccelli, Dr Bonsignore and Dr Landoni contributed to the planning of the work described in the article;

Dr Frontera, Dr Baccelli, Dr Nesti, Dr Tunzi, Dr Bonsignore, Dr Camaioni, Dr Notarstefano contributed to the conduct of the work described in the article;

Dr Frontera, Dr Baccelli, Dr Sacher, Dr Mahida, Dr Vlachos, Dr Derval, Dr Jais, Dr Hocini contributed to the reporting of the work described in the article;

Dr Frontera is responsible for the overall content as guarantor.

Figures

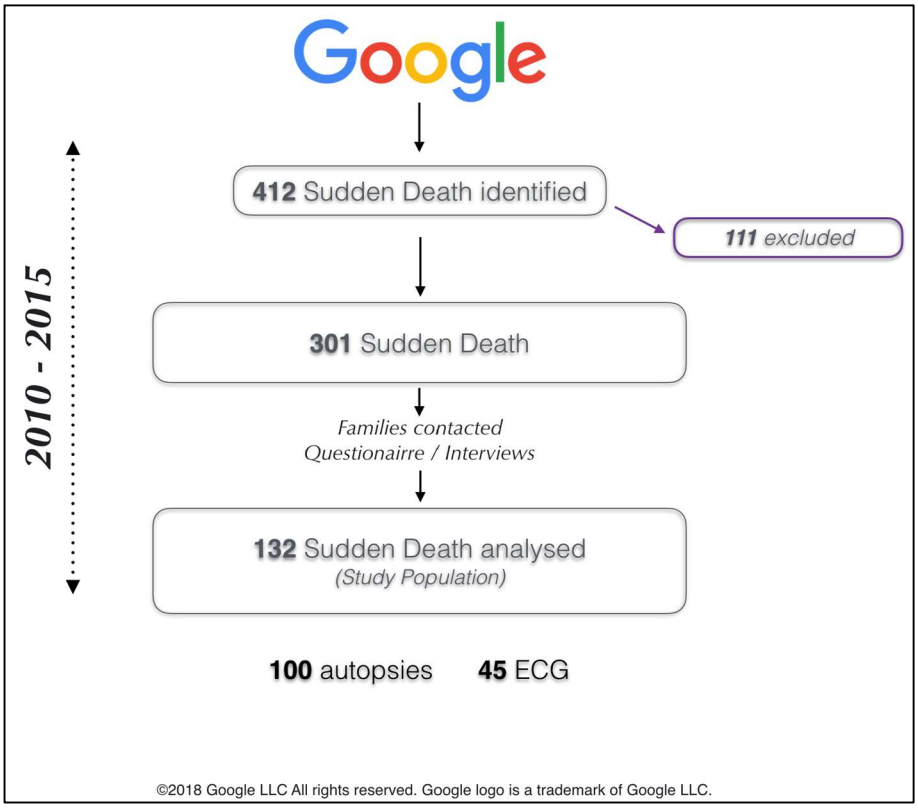

Figure 1. Cases of Sudden Death. Amongst the 412 SD identified through google search module, 111 were excluded because were toxicology positive, or were cases of homicide/suicide. Our analysis focused on 301 sudden death: families were contacted and data collected.

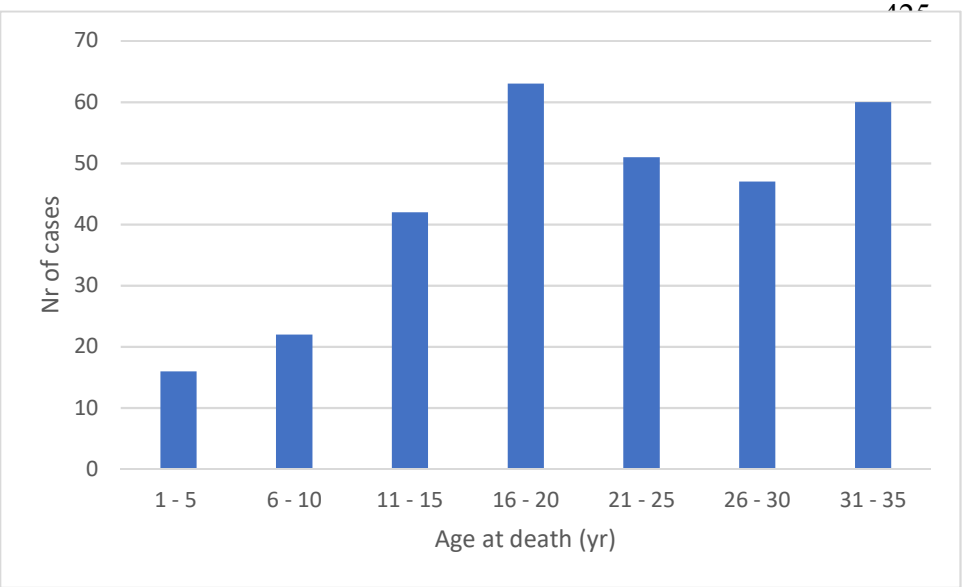

Figure 2. Sudden death according to age group (N=301)

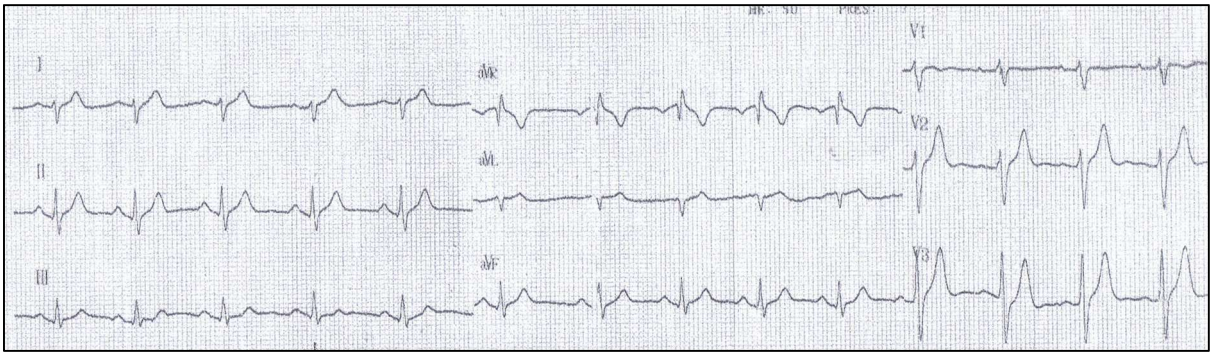

Figure 3, supplementary material. 12 leads ECG of the victim with short QT interval

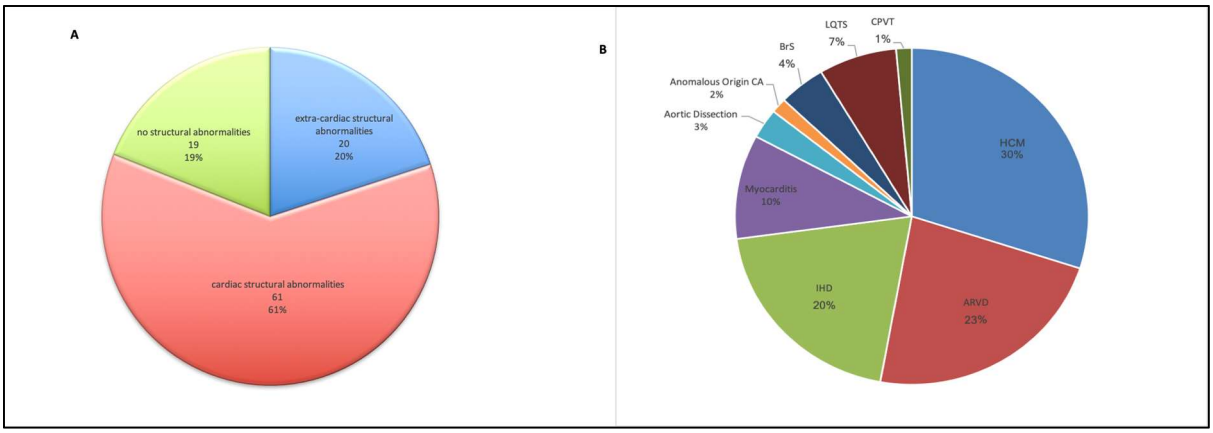

Figure 4. Left and right panel respectively show causes of sudden death and of sudden cardiac death. IHD: ischemic heart disease, HCM: hypertrophic Cardiomyopathy, ARVD: arrhythmogenic right ventricular dysplasia, MYO: myocarditis, BrS: Brugada Syndrome, LQTS: Long QT Syndrome, CPVT: Catecholaminergic Polymorphic Ventricular Tachycardia

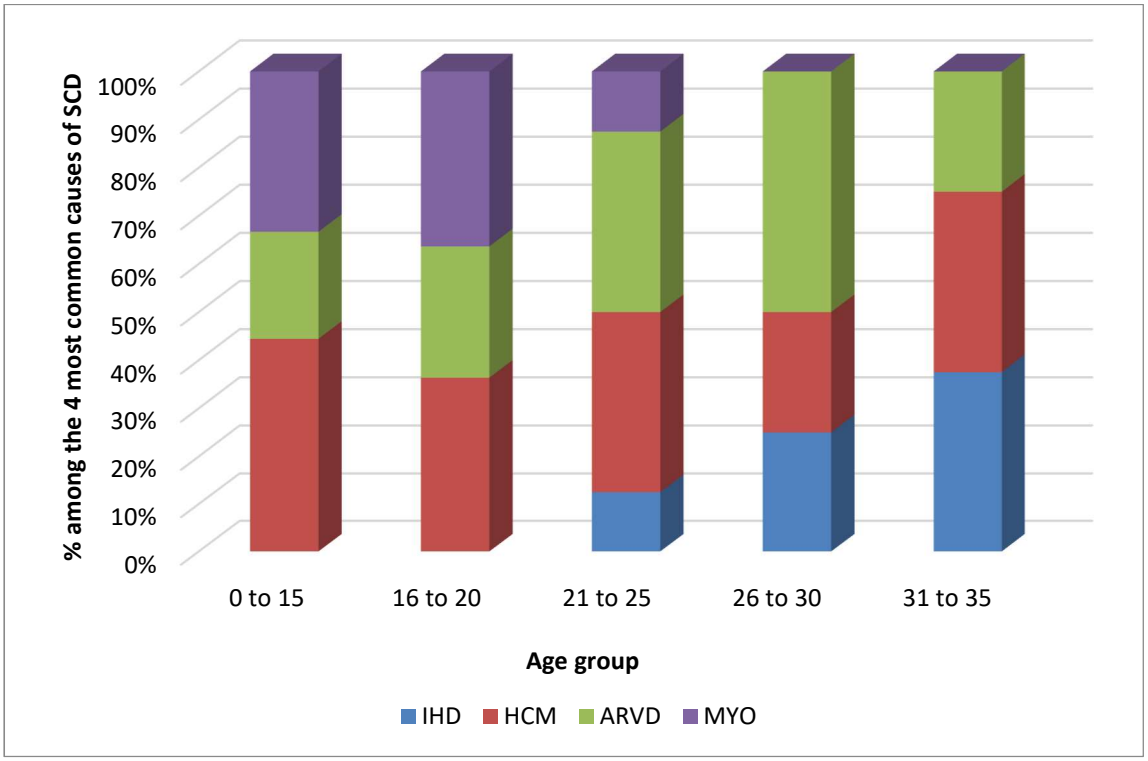

Figure 5. Trends of the 4 most common causes of SCD by age group. IHD: ischemic heart disease, HCM: hypertrophic Cardiomyopathy, ARVD: arrhythmogenic right ventricular dysplasia, MYO: myocarditis

SUPPLEMENTAL FIGURE 1

Supplemental figure 1. Excluded SD cases (n = 111)