Mafalda Carrington ORCID iD: 0000-0002-4491-5312

Antonio Creta ORCID iD: 0000-0002-7743-0143

Rui Providência ORCID iD: 0000-0001-9141-9883

High-risk features of unexplained syncope in the young

High-risk features and predictors of unexplained syncope in the young SCD-SOS cohort

Authors: Mafalda Carrington[1], MD, João Pais[1], MD, Diogo Brás[1], MD, Antonio Creta[2], MD, Rogério Teixeira[3], MD MSc PhD, Lino Gonçalves[3], MD MSc PhD, Rui Providência[2], MD MSc PhD.

[1]Cardiology department, Hospital do Espírito Santo de Évora, Portugal

[2]Barts Health NHS Trust, University College of London, St Bartholomew's Hospital, Barts Heart Centre, Farr Institute of Health Informatics, United-Kingdom

[3]Cardiology department of Centro Hospitalar Universitário de Coimbra, Faculdade de Medicina da Universidade de Coimbra, Portugal

Corresponding author: Mafalda Carrington, mafaldacarrington@gmail.com

Conflict-of-Interest: none declared.

Funding: none.

Data Availability Statement: data available on request from the authors and in article supplementary material.

Abstract

Introduction: The Sudden Cardiac Death-Screening of Risk FactOrS survey included a 12-lead ECG plus a digital-based questionnaire and aimed to screen for warning signs of diseases that may course with sudden cardiac death in children and young adults. We aimed to estimate the prevalence of unexplained syncope (US) and characterize its high-risk features and predictors in this cohort.

Methods&Results: We determined the most probable etiology of transient loss of consciousness (TLOC) episodes based on clinical criteria. US was an exclusion diagnosis and we analyzed its potential clinical and ECG predictors. Among 11,878 individuals, with a mean age of 21±6 (range 6-40) years-old, the cumulative incidence of TLOC was 26.5%, 76.2% corresponding to females. Reflex syncope was present in 66.4%, orthostatic hypotension in 8.2% and 14.8% of the individuals had US. Unexplained syncope was independently associated with age <18years-old (OR 1.695; 95%CI 1.26-2.29,p=0.001), male gender (OR 1.642; 95%CI 1.22-2.22,p=0.001), participation in competitive sports (OR 1.644;95%CI 1.01-2.66,p=0.043), syncope during exertion and/or palpitations preceding syncope (OR 2.556; 95%CI 1.92-3.40,p<0.001), syncope after exertion (OR 2.662; 95%CI 1.73-4.10,p<0.001), fever context (OR 9.606; 95%CI 4.13-22.34,p<0.001), isolated previous syncopal episode (OR 2.780; 95%CI 0.2.06-3.75,p<0.001) and history of palpitations requiring medical care (OR 1.945; 95%CI 1.14-3.31,p=0.014). We found no ECG predictors of US in this population.

Conclusions: The cumulative incidence of TLOC in children and young adults is high and remains unexplained in an important proportion of individuals. We identified eight clinical characteristics that may be useful for the risk stratification of individuals evaluated in a non-acute setting.

Keywords: transient loss of consciousness, unexplained syncope, predictors, children and young adults, athletes

Introduction

Sudden cardiac death (SCD) in the young population is relatively rare, with an estimated incidence of 0.46–3.7 events per 100 000 person-years among young adults (1)(2) and of approximately 7.8 per 100 000 persons during a 7-year period among children.(3) Yet, it remains an important health problem that frequently attracts *media* attention, as it frequently affects previously healthy individuals

and carries significant social and psychological consequences to the relatives of the victims. The viability, practicality and efficacy of screening programs is being put in question by some, as nearly two-thirds of the events occur as the first clinical manifestation of cardiac disease. (4)

The *SCD – Screening of Risk FactOrS* (SCD-SOS) survey aimed to screen for clinical and electrocardiographic warning signs of potential channelopathies and cardiomyopathies that may course with SCD in children and young adults. (5) A previous history of syncope is relevant in this setting, although routine assessment of this symptom through questionnaires has only been performed during pre-participation screening of young athletes. (6)

The differential diagnosis of cardiac syncope with other causes of transient loss of consciousness (TLOC) may be challenging, because TLOC is prevalent among young adults and it frequently has a benign prognosis. While several individuals present with a typical history of syncope with low-risk features that make the diagnosis of a reflex mechanism or orthostatic hypotension more likely, some syncopal events remain unexplained after initial evaluation. (7) On the other side, the identification of high-risk features in individuals with unexplained syncope (US) may suggest the presence of a serious underlying cause and help to distinguish which patients warrant further investigation and monitoring. Studies assessing high-risk features and clinical predictors of US in the general children and young adult population are lacking. We aimed to estimate the prevalence of US and characterize its high-risk features and predictors in the SCD-SOS cohort.

Methods

Design and study population From February 2012 to May 2013, 14 667 children and young adults (aged 40 years-old or less) of the central region of Portugal participated in the SCD-SOS survey (NCT01845909). It included a 12-lead ECG and a previously validated (5) questionnaire about symptoms, personal and family history that was filled by 11878 patients willing to provide more information (**Supplementary Material 1**). The SCD-SOS protocol was approved by the local Ethics Committee (355/Sec/10/03/2011), Comissão de Ética do Centro Hospitalar de Coimbra, Instituto Português do Ritmo Cardíaco e Comissão Nacional de Protecção de Dados.

SCD-SOS Survey and etiologic evaluation This was a detailed, digital-based, self-administered questionnaire, mainly composed of multiple-choice questions and few boxes allowing participants to provide additional details on their answers. It deemed to explore relevant clinical characteristics in the setting of SCD risk, and detect syncope related to potential causes of SCD. Based

on the answers provided (**Supplementary Material 1**), we were able to determine the most probable etiology of the TLOC episodes reported. According to the 2018 ESC syncope guidelines, (7) reflex syncope, either vasovagal or situational, was assumed in individuals who reported an episode precipitated by pain, emotion, fear, warm environment, or standing, with or without at least one typical progressive prodrome (pallor, sweating, and/or nausea). Orthostatic hypotension was presumed if syncope after or while standing was described in the absence of any of the previous prodromes, or if volume depletion was presumed based on the specifications provided (post-surgery, after donating blood). The remaining causes were ascertained based on the features ticked by the participants and US was an exclusion diagnosis if any of the previously described criteria were not satisfied (**Figure 1**). In addition, we were able to perform a risk stratification of the syncopal event based on the presence of 4 high-risk features (7) that were included in the multiple-choice questionnaire: 2 minor - no warning symptoms and a family history of SCD at young age; and 2 major – syncope during exertion and palpitations immediately preceding syncope. Participants could specify whether there were contexts or precipitating factors other than the ones listed in the questionnaire in a blank field. This allowed to classify the cases in which head trauma or other diseases were the causes of TLOC. We did not consider TLOC related to other disease when only "fever" was specified in the blank field.

Participants also provided information on whether they were physically active, the type of sports and number of hours practiced per week. There were questions on whether they had already practiced competitive or semi-professional sports, and on the timing and duration of competition. The type of exercise was specified in a box by each participant, thus allowing the classification of sports into 9 levels of static and/or dynamic components, based on previously-described hemodynamics and cardiac adaptations of athletes who compete in each type of exercise. (8) In the case of individuals who specified more than one modality (maximum of three), all were individually considered for the purpose of this analysis.

Finally, we studied potential predictors related to past medical history. Besides from screening for past personal history of palpitations, the questionnaire included information about relevant personal and family history of cardiac disease, as well as specific cardiac diagnosis in a multiple-choice format.

12-lead ECG analysis A 12-lead ECG was performed in supine position using a Mortara ELI 10 Portable Resting ECG machine (Mortara Instrument, Milwaukee, Wisconsin, USA) with a paper speed of 25 mm/s and amplification of 0.1 mV/mm. The heart rate, QRS duration, PR and QT interval

were registered using the recorder's automatic measurement software (VERITAS ECG algorithm, Mortara Instrument). The QT corrected (QTc) interval was also automatically obtained using the *Fridericia* correction, which was preset in the device and was previously validated, as described in a paper published by our group. (5) And the *Bazett* formula (QTc=QT/square root of RR interval) was calculated based on the automatic QT and RR intervals. The ECG of individuals who reported a TLOC episode were manually revised by 4 authors (MC, DB, JP and RP) and the following features were registered: atrioventricular (AV) block, incomplete and complete right and left bundle branch block (RBBB and LBBB), left (-30º to -90º) and right (>90º) axis deviation, ventricular preexcitation and number of premature ventricular complexes (PVCs). Left ventricular hypertrophy (LVH) was defined according to the presence of either Sokolow-Lyon (S in V1 + R in V5 or V6 ≥35mm) or Cornell criteria (S in V3 + R in aVL ≥20mm in men and ≥28mm in woman) and analysis for associated pathologic ECG findings was performed in the cases that fulfilled the voltage criteria. (9)

Statistical analysis We performed statistical analysis using Stata 13.0 software. Categorical variables were described as numbers of cases and percentages, and continuous variables as means ± standard deviation or medians [interquartile ranges] (as appropriate). We used qui-squared tests to determine whether the presence of clinical and ECG features differed between individuals with US and the remaining causes of TLOC. To express the strength of these relations, we obtained the odds ratios (OR) with 95% confidence intervals (CI) through univariate logistic regression for the outcome US. To compare the distribution of continuous variables between individuals with US and the remaining causes of TLOC, we used Student's t-test or a non-parametric alternative (Mann-Whitney) where appropriate. Multivariate logistic regression was used for establishing a US predictor model, using a forward selection method to include variables with the highest correlation with US, and considering the predictors with greater theoretical importance. Beta-coefficients were obtained for each variable in the model, based on which a score was calculated for each patient, rounding the coefficient to 0.5. Patients who scored 3 or more were interviewed by telephone by one of the investigators. A similar number of participants with a score of less than 3 were also contacted. Syncope recurrences, Cardiology exams and specialist consultations were ascertained. A p-value < 0.05 was regarded as significant and two-tailed tests were applied.

Results

Among the 11,878 individuals who participated in the survey both by undergoing an ECG and answering to the questionnaire, we calculated a mean age of 21±6 years-old, ranging from 6 to 40 years-old, of whom 22.3% were children (<18 years-old), and 59.6% (n=7078) were female. We found a cumulative incidence of TLOC of 26.5% (n=3153), 7.6% (n=22/289) in children less than 13 years-old, 20.2% (n=478/2364) in children between 13 and 17 years-old, 28.7% (n=2562/8919) in young adults with 18-35 years-old and 29.7% (n=91/306) in adults with 36-40 years-old (OR 1.588; 95%CI 1.46-1.73,p<0.001). The majority of participants with TLOC were female (76.2%, n=2403) and almost half (43,9%, n=1379) were engaged in regular physical activity.

Among individuals with a history of TLOC, 2095 (66.4%) had reflex syncope and 259 (8.2%) reported episodes compatible with orthostatic hypotension. Several other causes for the TLOC episodes were identified: 122 (3.9%) other diseases (ex: anemia, diabetes), 120 (3.8%) drugs/alcohol, 53 (1.7%) head trauma and 40 (1.3%) epileptic seizures (**Figure 1**).

We found a history of US in 466 participants (14.8%), 9 (40.9%) in young children under 13, 103 (21.6%) in children under 18, 355 (13.1%) in young adults and 19 (20.9%) in adults with 35-40 years-old (OR 0.625; 95%CI 0.51-0.77,p<0.001). Among individuals with US, 33.9% were males, versus 22.0% in the non-US group (OR 1.815; 95%CI 1.47-2.24,p<0.001), 34.8% had at least 1 major high-risk feature (OR 2.047; 95%CI 1.66-2.53,p<0.001) and 7.3% had 2 of these features. There were no statistically significant differences in major high-risk features among individuals in different age strata (OR 0.861; 95%CI 0.71-1.04;p=0.119). Participants having syncope with minor features were considered high-risk only if associated with abnormal ECG. (7) Although no particular ECG changes were found in participants with syncope and sudden death in relatives younger than forty years-old, there were 7 (0.2%) individuals with a TLOC event who had abnormal ECGs (Table 2).

Further information on the syncope high-risk features, as well as on relevant personal and familiar medical history are provided in **Table 1**. Regarding ongoing medication, we found no association between psychiatric drugs and US (4.1% vs 5.0%, OR 0.804; 95%CI 0.49-1.31,p=0.382). However, we observed an association between oral anticonceptive agents and reflex syncope (OR 1.479; 95%CI 1.32-1.66, p<0.001) and orthostatic hypotension (OR 1.530; 95%CI 1.14-2.05, p=0.005).

Syncope associated with fever was detected in 3.9% (n=18) of the individuals with US, comparing to 0.6% (n=17) of the individuals with the remaining causes of TLOC (OR 6.310; 95%CI 3.23-12.34, p<0.001). Among those with US associated with fever, four had an rSr' pattern in V1-V2

precordial leads with an r'-wave >2mm suggestive of non-Type 1 Brugada Pattern (T1BrP), and one had an ECG suggestive of T1BrP. Drug provocative testing was not performed in individuals with non-T1BrP, therefore the diagnosis was not confirmed. In total, only five individuals presented with a ventricular pre-excitation pattern (**Supplementary Material 2 and 3** for the ECGs), four of which described a syncopal episode compatible with reflex vasovagal syncope and one reported syncope in a context of disease. Further resting ECG comparisons between participants with US and other causes of TLOC are depicted in **Table 2**. Incomplete RBBB was the most frequent conduction perturbance detected (in 15.2% of the cases), followed by 1st degree AV block (in 1.0%, with a maximum PQ interval of 292ms). There were eleven individuals with complete RBBB, one individual with complete AV block, two with 2nd degree Mobitz I and 1 with sinus arrest. We identified no individuals with syncope and LBBB. LVH voltage ECG criteria were detected in 11.8% of the individuals with US, comparing to 8.1% of the remaining causes of TLOC (Table 2). Additional features commonly associated with pathological LVH such as T-wave inversion, ST-segment depression and pathological Q-waves were present in only 3.3% of the participants with voltage criteria and any TLOC episode. In total, we found that at least 0.8% (n=26, corresponding to 1,3% of participants with unexplained syncope and 0.7% with remaining causes of TLOC, p=0.231) of the participants who reported any past TLOC event presented abnormalities in the resting ECG that can be considered unrelated to regular training or expected physiologic adaptation to exercise and may require further diagnostic investigation. (9)

During the period of implementation of the SCD-SOS survey, high-risk patients were identified and referred for a Cardiology consultation at the National Services Hospital. The case of T1BrP who had a history of US received an implantable cardioverter-defibrillator, as did a patient who was diagnosed with hypertrophic cardiomyopathy. Although we do not have a complete follow-up of patients with syncope (only the individuals with high-risk features were identified and studied), we are currently raising funding to perform this study and present this analysis in future articles.

Among participants in whom a follow-up interview was possible by telephone (n=72), US was associated with a higher probability of having a cardiac diagnosis or cardiac exams with changes that could be related to a cardiac syncope, comparing to other causes of TLOC (63.6% vs 36.4%, OR 4.922; 95%CI 1.27-19.1, p=0.021). Among participants with US, one mentioned a *"complicated cardiac diagnosis"* that the patient did not want to disclose, one had a diagnosis of WPW after having US

during swimming practice, and underwent successful catheter ablation, four referred a diagnosis of mitral valve prolapse, three of them had US with associated extrasystole and one had a heart murmur with echocardiographic changes requiring annual follow-up. Among those with other causes of TLOC, one individual who reported a reflex syncope in the questionnaire had a WPW and underwent successful catheter ablation, two mentioned extrasystoles in 24-hour Holter, and another patient denoted previous Pediatric Cardiology follow-up due to ventricular hypertrophy confirmed on echocardiogram, that had reverted in an echocardiogram performed in adult age (possibly related to physical conditioning and deconditioning).

On a multivariate analysis, the variables that remained independently associated with US were age<18 years-old, male gender, participation in competitive sports, syncope during exertion and/or palpitations preceding syncope, syncope after exertion, isolated previous event and fever context and a history of palpitations requiring medical care. This model which included eight variables had a modest accuracy (C-statistics of 0.707; 95%CI 0.69-0.73) (**Table 3**). Twenty-five (45.4%) individuals who scored 3 or more in the model were reachable by telephone. Among them, 7 (63.6%) reported a cardiac diagnosis or exam changes, compared with 4 (36.4%) individuals with a lower score (OR 4.181; 95%CI 1.09-16.06, p=0.037). Finally, the electrocardiographic parameters that have shown differences in the univariate analysis were not independent predictors of US.

Discussion

The cumulative incidence of TLOC among young adults (28.8%) and children (18.9%) from the SCD-SOS survey is high. Unexplained syncope was present in 14.8% of the individuals and it was independently associated with age<18 years-old, male gender, participation in competitive sports, during exertion and/or palpitations preceding syncope, syncope after exertion, fever context, isolated previous syncopal episode and a history of palpitations requiring medical care. This model had a modest accuracy to predict US, and a total score of 3 or more (Table 3) was associated with reported cardiac diagnosis or significant exam changes. These variables may be regarded as potential warning signs in individuals who are evaluated in a non-acute setting. Additionally, ECG abnormalities in this population with TLOC are rare and could not be independently associated with US.

Syncope is a common medical problem that affects individuals of all ages and is most frequently recognized as a benign event. (7) However, most of the previous studies of syncope were conducted in emergency departments or hospitals, and evidence about incidence and causes is lacking

in the general population. In Italy, in a cohort of elderly patients admitted to an emergency department due to TLOC, (10) Rosso et al. found that 67% had reflex syncope, 10% had orthostatic hypotension and 15% had confirmed cardiac syncope. Accordingly, in a paper previously published by our group, (11) the majority of young adults presenting with a TLOC episode, reported pre-syncopal symptoms and a context that was suggestive of a benign (non-cardiac) etiology. (7) In our SCD-SOS cohort, the majority of TLOC episodes were also benign. US was present in 14.8% and it was associated with major and minor high-risk clinical features, thus suggesting the presence of a serious underlying cause and a higher likelihood of a cardiac syncope. (7) Marijon et al. have shown that warning symptoms are frequent prior to sudden cardiac arrest, but the vast majority of them are not acted upon. (12) Particularly in SCD associated with sports activity, one third of patients present with symptoms prior to the event, thus enhancing the importance of educational approaches to decrease the incidence of sports-associated SCDs. (12)(13) This evidence has triggered the acknowledgement of a new front in the fight against SCD - anticipation based on warning symptoms. (14) Therefore, we consider that early symptoms characterization and identification of the clinical features associated with US may contribute to improve outcomes related to SCD. We believe that the correct identification of patients at higher risk for SCD may lead to the creation of tools that can be used by emergency and pre-hospital medical services to stratify and manage these patients, similarly to what has been done to identify patients with ST-elevation myocardial infarction who are more likely to develop cardiac arrest before hospital arrival. (15)

We found that male gender and less frequent syncopal events were independent predictors of unexplained syncope. Ungar et al. have reported that, in patients referred to the emergency department following a syncopal event, (16) male gender increased and the incidence of syncopal recurrences decreased mortality. On the other side, coherent with our results, in the Italian cohort, palpitations preceding syncope, the absence of autonomic prodromes and syncope during exertion were also considered independent predictors of cardiac syncope. (10) In our cohort, the presence of typical symptoms was used to classify other causes of TLOC, therefore we excluded the high-risk feature absence of warning symptoms from the multivariate analysis to avoid potential information bias.

Our findings showing that participation in competitive sports and the occurrence of syncope during exertion were independent predictors of US, may be difficult to interpret in the light of the current knowledge. Previous authors described that syncopal episodes in young athletes are in most

cases non-cardiac and of reflex origin. (6) Additionally, in a Danish nationwide retrospective study in young adults, Risgaard et al. found no differences in the incidence rate of SCD between competitive and non-competitive athletes aged 12-35 years.(17) On the other side, coherent with our results, there is some evidence showing that exertional syncope tends to be more frequently associated with structural heart disease and with an unfavorable outcome in adults (18) and mainly with channelopathies and other rhythm disorders in children. (19) Stronger evidence supports an association between SCD and sports practice, namely among athletes in the Veneto region, in whom 91% of the SCDs occurred during sports activity or immediately afterward. And in a recent British post-mortem study on the etiology of SD in sports, which included 69% of competitive-athletes, showing that the majority of athletes died during exertion (61%). (20)

Another independent predictor of US in our cohort was an history of fever related-syncope. Some of these individuals had ECG features potentially suggestive of Brugada patterns. Previous studies suggested a higher risk of fever-related symptoms and arrhythmic events in children and young adults with Brugada Syndrome. (21) Finally, even though the ECG changes in a cohort of young adults with a high proportion of athletes may be difficult to interpret, at least 0.8% of the participants had abnormalities in the ECG that may require further assessment to exclude the presence of intrinsic cardiac disease. (9) There was a negative association between US and *Fridericia* and *Bazett* QTc, and a positive association with left ventricle hypertrophy in the baseline ECG in the univariate analysis, but after adjustment no ECG predictors of US were identified in the multivariate analysis. We hypothesize that for a cohort composed of predominantly healthy individuals, a much bigger sample would be necessary to further explore electrocardiographic predictors of US. More individuals would likely expand the statistical power of the sample and allow those analyses. However, this also appears to suggest that the effect size of frequent ECG traits as predictors of US is low.

The observed association between oral anticonceptive agents and reflex syncope in our cohort may be explained by the fact that women with menstrual irregularities or abundant menstrual hemorrhage, and who are thought to be more prone to have neurocardiogenic syncope as a result of that, (22) get treated more frequently with oral anticonceptives.

We estimate that the costs for the Portuguese Health Services to screen 11 878 participants in the SCD-SOS survey would be 79 207,00€ (2000,00€ for the software and for placing online the questionnaires plus 6,50€ per ECG (*Diário da República* 173/2018, Série I de 2018-09-07,

https://data.dre.pt/eli/port/254/2018/09/07/p/dre/pt/html)). Given that the survey allowed the diagnosis of US in 466 individuals and the identification of relevant ECG abnormalities in 26 participants, the estimated cost per diagnosis for a diagnostic yield of 4.1% is 160,99€. In our opinion, this is an acceptable cost for identifying patients who are at risk of developing cardiac diseases and/or have the potential to suffer SCD, thus warranting further investigations and follow-up.

Limitations

There are some limitations to our study which we need to emphasize. First, the cross-sectional nature of our data implies that the characterization of the syncopal event, personal and familiar history may be subject to recall bias, and this may be particularly true for children participating in the survey. Yet, we had a cohort of the general population of large dimensions, to which we applied a digital-based questionnaire mainly composed of closed questions and few open fields, thus enhancing our ability for complete data collection. Second, our questionnaire did not allow to establish a temporal relationship between syncope and fever or the type or quantity of physical exercise since the inclusion of such questions would have increased the complexity of the questionnaire. Third, we studied a young adult cohort with children and young adults (<40 years-old), which included both athletes and non-athletes, therefore our findings should only be applied to individuals belonging to these age strata. Finally, despite the clinical suspicion that individuals with US may be at an increased risk for adverse cardiovascular events, we cannot make the definite diagnosis of cardiac syncope or directly infer the risk of SCD based on our data, given the cross-sectional nature of our study. Yet, we interviewed by telephone 72 participants and found that those with a previous US episode had more frequently a cardiac diagnosis or exam change requiring follow-up than patients with other causes of TLOC.

Conclusions

The cumulative incidence of TLOC in children and young adults is high and it remains unexplained in a significant proportion of individuals. We identified eight clinical characteristics that may be regarded as potential warning signs in a non-acute setting. Further studies are needed to establish whether this screening approach may lead to reduction of cardiac events in this population.

References

1. Maron BJ, Gohman T, Aeppli D. Prevalence of Sudden Cardiac Death During Competitive Sports Activities in Minnesota High School Athletes. J Am Coll Cardiol. 1998;32(7):1881–4.

2. Werf C, Hendrix A, Birnie E, Bots M, Vink A, Bardai A et al. Improving usual care after

sudden death in the young with focus on inherited cardiac diseases (the CAREFUL study): a community-based intervention study. Europace. 2016;18:592–601.

3. Winkel BG, Risgaard B, Sadjadieh G, Bundgaard H, Haunsø S, Tfelt-Hansen J. Sudden cardiac death in children (1-18 years): Symptoms and causes of death in a nationwide setting. Eur Heart J. 2014;35(13):868–75.

4. Basso C, Aguilera B, Banner J, Cohle S, Amati G, Gouveia R. Guidelines for autopsy investigation of sudden cardiac death: 2017 update from the Association for European Cardiovascular Pathology. Virchows Arch. 2017;471:691–705.

5. Providência R, Karim N, Srinivasan N, Honarbakhsh S, Vidigal-Ferreira M, Gonçalves L et al. Impact of QTc formulae in the prevalence of short corrected QT interval and impact on probability and diagnosis of short QT syndrome. Heart. 2018;104(6):502–8.

6. Colivicchi F, Ammirati F, Santini M. Epidemiology and prognostic implications of syncope in young competing athletes. Eur Heart J. 2004;25:1749–53.

7. Brignole M, Moya A, Lange F, Deharo J-C, Elliott P, Fanciulli A et al. 2018 ESC Guidelines for the diagnosis and management of syncope The Task Force for the diagnosis and management of syncope of the European Society of Cardiology (ESC). Eur Heart J. 2018;39(June):1883–948.

8. Levine B, Baggish A, Kovacs R, Link M, Maron M. Eligibility and Disqualification Recommendations for Competitive Athletes With Cardiovascular of Sports: Dynamic, Static, and Impact and American College of Cardiology. Circulation. 2015;132:262–6.

9. Sharma S, Drezner J, Baggish A, Papadakis M, Borjesson M, Salerno J et al. International Recommendations for Electrocardiographic Interpretation in Athletes. J Am Coll Cardiol. 2017;69(8):1057–75.

10. Rosso A, Ungar A, Maggi R, Giada F, Petix N, Santo T et al. Clinical predictors of cardiac syncope at initial evaluation in patients referred urgently to a general hospital: the EGSYS score. Heart. 2008;94:1620–6.

11. Providência R, Silva J, Mota P, Nascimento J, Leitão-Marques A. Transient loss of

consciousness in young adults. Int J Cardiol. 2011;152(1):139–43.

12. Marijon E, Uy-Evanado A, Dumas F, Karam N, Reinier K, Teodorescu C et al. Warning Symptoms Are Associated With Survival From Sudden Cardiac Arrest. Ann Intern Med. 2017;176(5):139–48.

13. Marijon E, Uy-Evanado A, Reinier K, Teodorescu C, Narayanan K, Jouven X et al. Sudden Cardiac Arrest During Sports Activity in Middle Age. Circulation. 2015;131(16):1384–91.

14. Karam AN, Marijon E, Dumas F, Offredo L, Beganton F, Bougouin W et al. Characteristics and Outcomes of Out-of-Hospital Sudden Cardiac Arrest According to the Time of Occurrence. Resuscitation. 2017;

15. Karam N, Bataille S, Marijon E, Giovannetti O, Tafflet M, Savary D et al. Identifying Patients at Risk for Prehospital Sudden Cardiac Arrest at the Early Phase of Myocardial Infarction: The e-MUST Study (Evaluation en Médecine d'Urgence des Stratégies Thérapeutiques des infarctus du myocarde). Circulation. 2016;134(25):2074–83.

16. Ungar A, Rosso A, Giada F, Bartoletti A, Furlan R, Quartieri F et al. Early and late outcome of treated patients referred for syncope to emergency department: the EGSYS 2 follow-up study. Eur Heart J. 2010;31:2021–6.

17. Risgaard B, Winkel B, Jabbari R, Glinge C, Ingemann-hansen O, Thomsen J et al. Sports Related Sudden Cardiac Death in a Competitive and Non-competitive Athlete Population aged 12-49 years: Data from an unselected Nationwide study in Denmark. Hear Rhythm. 2014;11(10):1673–81.

18. Corrado D, Basso C, Pavei A, Michieli P, Schiavon M, Thiene G. Trends in Sudden Cardiovascular Death in Young Competitive Athletes. JAMA. 2015;296(13):1593–601.

19. Miyake CY, Motonaga KS, Fischer-Colbrie ME, Chen L, Hanisch DG, Balise RR et al. Risk of cardiac disease and observations on lack of potential predictors by clinical history among children presenting for cardiac evaluation of mid-exertional syncope. Cardiol Young. 2016;26(5):894–900.

20. Finocchiaro G, Papadakis M, Robertus J, Dhutia H, Steriotis A, Tome M et al. Etiology of

Sudden Death in Sports. J Am Coll Cardiol. 2016;67(18):2108–2015.

21. Michowitz Y, Milmn A, Andorin A, Sarquella-Brugada G, Corcia M, Gourraud J-B et al. Characterization and Management of Arrhythmic Events in Young Patients With Brugada Syndrome. J Am Coll Cardiol. 2019;73(14):1756–65.

22. Frazier JP, Yetman RJ, Huang D. Syncope in adolescent girls. Clin Pediatr (Phila). 2001;40(8):457–60.

23. Committee A, Society R. AHA / ACCF / HRS Scientific Statement AHA / ACCF / HRS Recommendations for the Standardization and Interpretation of the Electrocardiogram Part IV: The ST Segment, T and U Waves, and the QT Interval A Scientific Statement From the American Heart Associ. 2009;241–50.

Table 1: Comparison of individuals with US and other causes of TLOC

	Any past TLOC event (N=3153)	Unexplained syncope (n=466)	Remaining causes of TLOC (n=2687)	OR (95%CI)	p-value
Anthropometric characteristics					
Male gender	23.8% (750)	33.9% (158)	22.0% (592)	1.815 (1.47-2.24)	**<0.001**
Children (<18 years-old)	15.6% (493)	24.0% (112)	14.4% (388)	1.875 (1.48-2.38)	**<0.001**
Body mass index (kg/m²)	22.0±3.2	22.5±3.4	22.0±3.2	1.045 (1.02-1.08)	**0.002**
Physical activity					
Sports practice	43.9% (1379)	46.9% (217)	43.4% (1162)	1.149 (0.94-1.40)	0.168
Duration (in hours per week)	3[2-6]	4[2-6]	3[2-5]	1.021 (0.98-1.06)	0.243
Competitive sports practice	37.3% (1013)	43.0% (179)	36.2% (834)	1.328 (1.07-1.64)	**0.009**
Duration (in years)	4[3-7]	4[3-7]	4[2-7]	1.008 (0.96-1.05)	0.731
Moderate to high static and dynamic components	44.2% (1393)	47.2% (220)	43.6% (1173)	1.154 (0.95-1.41)	0.154
Syncopal event risk features					
Major high-risk features (7) - *at least 1:*	22.7% (717)	34.8% (162)	20.7% (555)	2.047 (1.66-2.53)	**<0.001**
During exertion	8.8% (278)	24.7% (115)	6.1% (163)	5.073 (3.90-6.60)	**<0.001**
Palpitations preceding syncope	16.6% (521)	17.4% (81)	16.4% (440)	1.074 (0.83-1.39)	0.589
Minor high-risk features (7) - *at least 1:*	16.6% (523)	28.5% (133)	14.5% (390)	2.352 (1.87-2.95)	**<0.001**

No warning symptoms	15.3% (481)	26.6% (124)	13.3 (357)	2.366 (1.87-2.99)	**<0.001**
Sudden death in relatives <40 years-old	1.5% (47)	2.2% (10)	1.4% (37)	1.588 (0.78-3.22)	0.199
Syncope after exertion	6.5% (206)	12.9% (60)	5.4% (146)	2.572 (1.87-3.54)	**<0.001**
Intense malaise preceding syncope	31.1% (981)	19.4% (77)	32.8% (904)	0.528 (0.42-0.67)	**<0.001**
Fever-related syncope	1.1% (35)	3.9% (18)	0.6% (17)	6.310 (3.23-12.34)	**<0.001**
Recurrence of syncope (nº of events)	1.4±0.5	1.3±0.5	1.5±0.5	0.496 (0.39-0.63)	**<0.001**
Syncope with resulting injury	9.8% (298)	10.4% (45)	9.8% (253)	1.073 (0.77-1.50)	0.679
Past personal and familiar medical history					
Palpitations with syncope or presyncope	5.9% (187)	7.7% (36)	5.6% (151)	1.406 (0.96-2.05)	0.077
Palpitations requiring medical assessment	4.12% (130)	5.8% (27)	3.8% (103)	1.543 (1.00-2.38)	**0.051**
Previous consultation with a Cardiologist	36.8% (1148)	41.3% (190)	36.0% (958)	1.250 (1.02-1.53)	**0.020**
*Known cardiac disease**	0.5% (15)	0.2% (1)	0.5% (14)	0.410 (0.05-3.13)	0.390
*Know cardiac disease in relatives**	3.0% (96)	1.3% (6)	3.4% (90)	0.376 (0.16-0.86)	**0.021**

Legend: *Specific cardiac diagnosis included in the questionnaire in a multiple-choice format: Hypertrophic Cardiomyopathy, Marfan Syndrome, Arrhythmogenic Right Ventricle Dysplasia, Dilated Cardiomyopathy, Left ventricle non-compaction, Aortic aneurysm, Wolff-Parkinson-White Syndrome, Abnormal origin of coronary arteries, Brugada Syndrome, Long QT Syndrome, Catecholaminergic tachycardia.

Table 2: High-risk features of individuals with US and other causes of TLOC

	Any past TLOC event (N=3153)	Unexplained syncope (n=466)	Remaining causes of TLOC (n=2687)	OR (95%CI)	p-value
Clinical major high-risk feature*	22.7% (717)	34.8% (162)	20.7% (555)	2.047 (1.66-2.53)	**<0.001**
Clinical minor high-risk feature+	0.2% (7)	0.2% (1)	0.2% (6)	0.961 (0.11-8.00)	0.971
Bradicardia ≤ 40 beats per minute	0.2% (6)	0.4% (2)	0.2% (4)	2.891 (0.53-15.83)	0.221
AV conduction system disease					
1st degree	1.0% (33)	0.9% (4)	1.1% (29)	0.794 (0.28-2.27)	0.666
2nd degree, Mobitz I	0.1% (2)	0.0% (0)	0.1% (2)	-	0.556
3rd degree	0.0% (1)	0.2% (1)	0.0% (0)	-	**0.016**
Incomplete RBBB	15.2% (478)	12.9% (60)	15.6% (418)	0.802 (0.60-1.07)	0.137
Complete RBBB	0.2% (8)	0.2% (1)	0.3% (7)	0.823 (0.10-6.71)	0.856

Left axis deviation	0.5% (16)	1.1% (5)	0.4% (11)	2.638 (0.91-7.63)	0.073
Right axis deviation	3.7% (116)	3.0% (14)	3.8% (102)	0.785 (0.44-1.38)	0.403
QTcorrected (*Fridericia *formula) ***QTcorrected (*Bazett *formula)***	393.4±17.1 403.9±22.2	391.5±17.8 401.7±22.5	393.8±16.9 404.2±22.1	0.992 (0.99-1.00) 0.995 (0.99-1.00)	**0.007** **0.021**
Short QTc* § (Fridericia *formula) ***Short QTc* § (Bazett *formula)***	2.0% (64) 2.2% (69)	3.9% (18) 3.2% (15)	1.7% (46) 2.0% (54)	2.307 (1.32-4.01) 1.622 (0.91-2.90)	**0.003** 0.103
Prolonged QTc* ** (Fridericia *formula) ***Prolonged QTc* ** (Bazett *formula)***	0.1% (4) 0.9% (29)	0.2% (1) 0.4% (2)	0.1% (3) 1.0% (27)	1.924 (0.200-18.54) 0.425 (0.10-1.79)	0.571 0.244
Short PR interval	5.4% (171)	4.7% (22)	5.6% (149)	0.844 (0.53-1.34)	0.469
Premature ventricular complexes (n≥2)	0.3% (10)	0.6% (3)	0.3% (7)	2.481 (0.64-9.63)	0.189
Left ventricle hypertrophy* ++** ***With ST-depression ***With T-wave inversion*** ***Sokolow-Lyon criteria (if age>16 yo)*** ***Cornell criteria (if age>16 yo)*** ***S-wave in V1 + R-wave in V6 (if age≤16 yo)***	21.6% (682) 2.2% (6) 0.7% (2) 28.6±8.5 11.8±5.9 22.8±7.2	27.7% (129) 0.0% (0) 0.0% (0) 29.7±9.3 12.5±6.0 23.7±6.9	20.6% (553) 2.8% (6) 0.9% (2) 28.4±8.4 11.7±5.9 22.6±7.3	1.482 (1.18-1.85) - - 1.0127(1.00-1.03) 1.021 (1.00-1.04) 1.02 (0.98-1.06)	 **0.001** 0.212 0.475 **0.005** **0.018** 0.303
Ventricular pre-excitation pattern	0.2% (5)	0.0% (0)	0.2% (5)	-	0.351
Type-1 Brugada pattern	0.0% (1)	0.2% (1)	0.0% (0)	-	**0.016**
***Non-Type 1 Brugada pattern*§§**	15.1% (475)	12.9% (60)	15.4% (415)	0.809 (0.60-1.08)	0.153

Legend:

* Syncope during exertion and/or palpitations preceding syncope, + syncope no warning symptoms, that was considered high-risk feature only if associated with abnormal ECG (7) § QTc <360ms, ** QTc >460ms in females, >450ms in males and > 450ms in children with less than 13 years-old independently of gender (23), ++Sokolow-Lyon criteria ≥ 35mm or Cornell criteria ≥ 20mm in men or ≥ 28mm in woman, §§ rSr' pattern in V1-V2 precordial leads with an r'-wave >2mm suggestive of non-Type 1 Brugada Pattern.

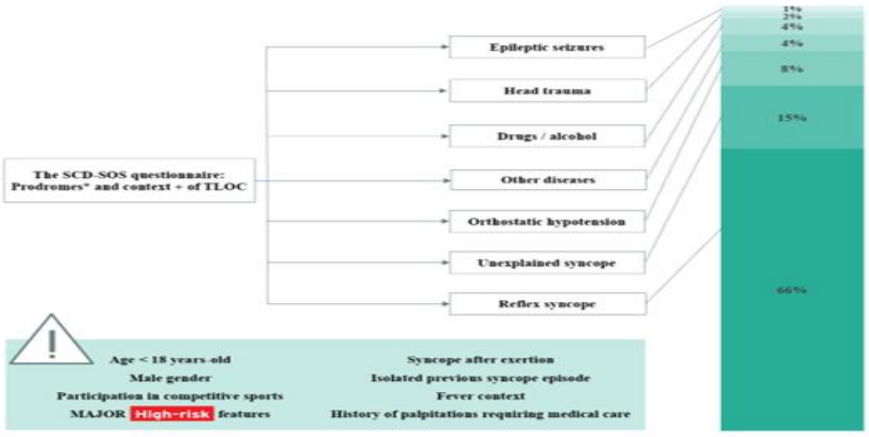
AV atrioventricular, CI confidence interval, ms milliseconds, OR odds ratio, QTc QT corrected, RBBB Right Bundle Branch Block, yo years-old

Table 3: Independent predictors of unexplained syncope

Independent predictors of US	OR	95%CI	p-value	β-coefficient	Score
Children (<18 years-old)	1.695	1.26-2.29	0.001	0.528	0.5
Male gender	1.642	1.22-2.22	0.001	0.496	0.5
Syncope during exertion and/or palpitations preceding syncope	2.556	1.92-3.40	<0.001	0.938	1
Syncope after exertion	2.662	1.73-4.10	<0.001	0.979	1
Isolated previous syncope episode	2.780	2.06-3.75	<0.001	1.022	1
History palpitations requiring medical care	1.945	1.14-3.31	0.014	0.665	0.5
Fever-related syncope	9.606	4.13-22.34	<0.001	2.262	2
Participation in competitive sports	1.644	1.01-2.66	0.043	0.497	0.5

Legend: OR odds ratio, CI confidence interval

Figure 1: Causes of TLOC and predictors of unexplained syncope in individuals below 40 years-old



Legend: *Prodromes: the presence of at least 1 symptom among pallor, sweating, and nausea was considered positive for prodromes and thus suggestive of reflex syncope in the presence of a typical context/precipitating factor. + Context: participants could provide 1 or more answers among 11 options and we used 9 of them for etiology classification. For reflex syncope: 1) fright/loud noise, 2) stress, 3) pain, 4) sight of blood/injection, 5) heat. For orthostatic hypotension: 7) prolonged standing. For

drugs/alcohol: 8) drugs and 9) alcohol. For other diseases (cases in which only fever was specified were not considered as disease) and head trauma: there was an additional blank field to specify other contexts or precipitating factors. This field also allowed to classify some of the previous etiologies. For epileptic seizures: the occurrence of seizures witnessed by others was specifically asked in the questionnaire. Unexplained syncope was considered if none of the previous criteria were met.