



Incidence and predictive factors of acute diseases in patients with syncope: the ESCAPE study

Filippo Numeroso¹ · Gianluigi Mossini¹ · Ilaria Grieco² · Marina Bergamin² · Marcello Maggio¹ · Giuseppe Lippi³ · Gianfranco Cervellin⁴

Received: 26 December 2020 / Accepted: 15 February 2021 / Published online: 18 March 2021
© Società Italiana di Medicina Interna (SIMI) 2021

Abstract

According to the 2018 ESC guidelines, emergency physicians shall primarily aim to identify syncopal episodes associated with an underlying acute principal disease. Therefore, in this study, we aimed to assess the incidence of syncope associated with acute principal diseases (APDs) and to identify predictive factors reflecting the presence of these underlying conditions. We retrospectively evaluated all patients presenting with syncope during a 6-month period to the local emergency department, collecting incidence of syncopal cases associated with APDs, personal information, clinical features, and laboratory abnormalities, which were compared between syncopal patients with or without APDs. A syncope-associated APD could be diagnosed in 346/1279 patients (27.1%). In the majority of cases, the cause was a non-cardiovascular acute condition (67%), mostly non-life-threatening such as infectious diseases (34.4%) and acute diseases with pain, fluid loss or hypotension (23.7%). Severe acute cardiovascular conditions were less frequent (4.2%). Cardiogenic syncope, no previous history of syncopal episodes, not full agreement with typical clinical features of syncope, alterations of vital parameters, and laboratory abnormalities were also found to be independently associated with syncope-associated APDs. Syncope may be frequently associated with APDs of varying severity, though mostly non-clinically threatening, thus confirming that this condition shall be considered a symptom and not a disease. Emergency physicians should hence be first engaged in troubleshooting an underlying pathology when facing patients with syncope, for timely identifying patients at higher risk of short-term adverse events and reducing inappropriate admissions and diagnostic investigations, especially in the presence of hypotensive syncope elicited by non-severe concurrent conditions.

Keywords Syncope · Acute diseases · Emergency department

Introduction

According to the 2018 European Society of Cardiology (ESC) Guidelines for diagnosis and management of syncope [1], emergency physicians (EPs) shall primarily aim

to identify syncopal episodes which may be a consequence or even exacerbate an underlying acute principal disease (APD), especially those associated with risk of rapid deterioration, since these will most frequently determine short-term adverse events rather than the syncope itself [2]. Moreover, as all forms of syncope (especially reflex and orthostatic) are more likely to occur or may be associated with higher severity, in the presence of various factors such as volume depletion (e.g., haemorrhage, low fluid intake, diarrhoea, vomiting) or pulmonary diseases causing brain oxygen supply reduction [1], EPs shall equally quickly identify all these possible predisposing factors, because they would occasionally already justify the onset of a syncopal episode, which have a benign and non-cardiac nature in many of such cases.

Blood tests abnormalities are frequent in patients with syncope [3], though the ESC guidelines conclude that they have limited role in risk stratification [1]. However, we

✉ Filippo Numeroso
fnumeroso@ao.pr.it

¹ Emergency Department, University Hospital of Parma, Via Gramsci 14, 43126 Parma, Italy

² Postgraduate School of Gerontology, University of Parma, Via Università 12, 43121 Parma, Italy

³ Section of Clinical Biochemistry, Department of Neuroscience, Biomedicine and Movement, University of Verona, Piazzale L.A. Scuro 10, 37134 Verona, Italy

⁴ Academy of Emergency Medicine and Care (AcEMC), Via Maugeri 10, 27100 Pavia, Italy

hypothesize that the role of laboratory investigations should be reevaluated, since most adverse outcomes are already present at Emergency Department (ED) admission [4–6]. Furthermore, clinical experience also suggests that most TLOC cases associated with APDs do not fully meet the typical clinical features of syncope (i.e., rapid onset, short duration, and spontaneous complete recovery), so that it is conceivable that a not full agreement with these typical features could also be used for identifying the possible presence of serious underlying illnesses. Notably, no published studies have recently addressed the framework of syncope secondary to underlying acute disease or the role of clinical features and laboratory investigations for identifying patients in whom syncope may only be an epiphenomenon or a symptom of an APD, to the best of our knowledge. Therefore, the main purposes of this study were: (i) assessing the incidence of syncope associated with APDs; (ii) identifying predictive factors reflecting the presence of APDs, by exploring the clinical characteristics and laboratory abnormalities of these cases in comparison with those found in syncopal patients without underlying acute conditions.

Methods

Study design and setting

This is a retrospective, observational, single-center study of patients evaluated for syncope during a 6-month period (between January and June 2019) at the ED of University Hospital of Parma, a large urban ED with over 80,000 annual visits.

Selection of participants

Patients evaluated for TLOC of suspected syncopal origin during the study period were anonymously identified from the hospital database, by searching ED charts, containing (i) the following triage symptoms or final diagnostic categories: loss of consciousness, syncope, fainting, collapse, light-headedness, dizziness, and unexplained falls, OR (ii) the following specific International Classification of Diseases-9 (ICD-9) codes: 780.2 Syncope and collapse; 780.02 Transient alteration of awareness; 780.09 Other alteration of consciousness; 992.1 Heat syncope. Two expert physicians carefully reviewed these preliminarily identified medical records, applying the following exclusion criteria (i) age < 18 years, (ii) syncope occurring > 24 h before ED presentation, (iii), no syncope, in case of inappropriate or inaccurate ED charts selection, (iv) other non-specific complaints, such as pre-syncope, vertigo, dizziness, light-headedness, or lack of information necessary for patient enrolment and diagnosis of any APD, (v) definite or highly

suspected diagnosis of non-syncopal TLOC (e.g., epilepsy, psychogenic pseudo-syncope, hypoglycaemia, unintentional falls in the elderly), and (vi) TLOC due to head injury or associated with major trauma. A third opinion was asked to resolve possible disagreement in data interpretation. Due to the retrospective process of selecting patients, pre-syncope could not be always considered as surrogate for syncope. Conversely, we preferred to evaluate cases individually, so that only patients displaying an aborted syncope could be enrolled, thus excluding those with non-specific, self-resolving (i.e., without any interventions, not even with sitting or lying down) symptoms.

Measures

The following data were collected by consultation of hospital medical records: (i) personal data (gender; age), (ii) history of heart diseases (coronary heart diseases or heart failure with reduced ejection fraction), (iii), history of previous episodes of syncope (iv), presence of witnesses during the syncopal event, (v) presence of APDs underlying the syncopal episode, (vi) ED classification of syncope, according to ESC guidelines [1] as cardiogenic, reflex, orthostatic hypotension or unexplained, (vii) presence of all typical features of syncope, namely rapid onset, short duration and spontaneous complete recovery, and (viii) disposition, classified as discharge from ED, hospital admission or death.

The presence of one or more of the following abnormalities of vital parameters was also recorded: systolic blood pressure ≤ 100 mmHg; heart rate < 50 or > 100 (at rest) bpm; respiratory rate > 30/min; pulse oximeter value (spO_2) < 95% (excluding patients with chronic respiratory failure); body temperature > 38 °C. The following laboratory abnormalities were considered, according to pre-existing evidence garnered from syncope literature [7] and standard reference ranges used in the local laboratory: anaemia (i.e., haemoglobin < 100 g/L, excluding patients with already known chronic anaemia); high leukocytosis (i.e., white blood cell count > $10 \times 10^9/L$); ion imbalances (i.e., serum potassium < 3.5 or > 5.5 mmol/L; serum sodium < 135 or > 148 mmol/L); abnormal blood urea nitrogen (i.e., > 50 mg/dL, excluding patients with already known chronic kidney disease), as well as increased values of D-dimer (i.e., > 250 ng/mL) and high-sensitivity cardiac troponin I (i.e., hs-cTnI > 17.8 ng/L in men and > 10.5 ng/L in women, respectively).

The type of APD was then classified as follows: (a) acute coronary syndrome; (b) major arrhythmias (such as sustained ventricular tachycardia, supraventricular tachycardia with hemodynamic instability, complete heart block or other critical bradyarrhythmias); (c) other acute cardiovascular events (such as acute heart failure, pulmonary embolism, aortic syndrome); (d) haemorrhage or anaemia requiring

blood transfusion; (e) acute neurological disorders; (f) internal acute diseases with pain, fluid loss or hypotension; and (g) infectious diseases. Notably, we considered as APD any acute medical condition with symptoms or signs already present upon ED admission, even when non-life-threatening, when a plausible pathophysiological relationship with syncope could be established, either as a direct cause or as a triggering factor. Finally, the most serious APD requiring therapeutic management in the ED was considered in our analysis when two or more of these conditions could be diagnosed. The identification of APDs underlying the syncopal episode was carried out by two expert physicians, whilst a third opinion was asked only for disagreement in data interpretation.

Statistical analysis

Since it was a retrospective study, the sample size was determined by local feasibility, as number of patients evaluated for syncope in the ED. All data were entered into an SPSS statistical file (V 21.0), analyzed with descriptive statistics (mean and standard deviation for the age, 95% proportion confidence interval for other variables), to summarize the various aspects of patients with APDs, and with chi-squared test (for categorical variables) and Student's *t* test (for continuous variables), for comparison with patients without underlying APDs. A further binary logistic regression was conducted, for identifying which variables could independently predict the presence of a syncope-associated APD.

The study was carried out in agreement with the Declaration of Helsinki and under the terms of all relevant local legislation. The study also received regulatory approval from the local ethical committee (Reference Number 0000749, 2/7/19) and was carried out according to local legislation [8], with considerable organizational restrictions due to current pandemic.

Results

Figure 1 shows the flow diagram of screened and enrolled population. From an initial number of 2679 ED medical charts assessed throughout the study period, 1279 patients (47.7% of initial cohort) were finally included in our analysis, 602 of whom were men (47.1%) and 677 women (52.9%), with a mean age 60.4 ± 22.4 years (18–104 years). Most of these patients had reflex or orthostatic syncope, and 73% could be discharged after ED evaluation (see Supplemental Table 1 for details). In this cohort of patients, 346 cases of syncope-associated APDs could be identified (27.1% of all patients enrolled), most of which were diagnosed in ED (e.g., in 81.1% of cases).

The clinical characteristics of patients with and without syncope-associated APD are summarized in Table 1. Compared to those without underlying conditions, those with syncope-associated APDs appeared to be older (mean age: 68.6 ± 19.8 vs. 57.2 ± 22.4 years; $p < 0.001$; patients > 70 years old: 59% vs. 35%; $p < 0.001$), though with equal gender distribution.

As concern medical history, heart diseases were more frequent in patients with APDs than in those without (21.4% vs. 12.0%; $p < 0.001$), whilst previous syncopal episodes were more frequent in patients with syncopal episodes which were not associated with APDs (27.2% vs. 43.8%; $p < 0.001$). No differences were found regarding the presence of witnesses during the syncopal episode. In patients with APDs, syncope was found to be more frequently cardiogenic (16.8% vs. 4.1%; $p < 0.001$), orthostatic (32.4 vs. 21%, $p < 0.001$) or undetermined (32.1% vs 20.8%, $p < 0.0001$); in these patients, we more frequently found a not full agreement with typical clinical features (25.7% vs. 5.0%; $p < 0.001$). Reflex syncope was instead more frequent in patients without APDs (54.1% vs. 18.8%, $p < 0.001$). Patients with syncope-associated APDs more frequently had vital parameters (59.0% vs. 15.2%; $p < 0.001$) and laboratory (77.5% vs. 31.5%; $p < 0.001$) abnormalities. Patients with APDs were more frequently admitted compared to those without (62.1% vs. 12.4%; $p < 0.001$).

The range of APDs that could be diagnosed in our study population are summarized in Table 2. The more frequent ADPs were infectious diseases (34.4% overall, mostly encompassing pneumonia, acute viral illnesses with fever and sepsis), APDs with pain, fluid loss or hypotension (23.7% overall, mostly entailing gastroenteritis, painful acute abdominal diseases, fluid loss due to metabolic or renal disease or heat-related), along with other cardiovascular events (12.1% overall, mostly encompassing heart failure with reduced ejection fraction and pulmonary embolism). Further details are provided in Supplemental Table 2, whilst laboratory abnormalities are detailed in Supplemental Table 3. Importantly, the test with the highest negative predictive value was D-dimer (84%), followed by hs-cTnI (81%) and BUN (80%), whilst hemoglobin had the highest positive predictive value (72%).

Table 3 shows the result of binary logistic regression, where the presence of APD was entered as dependent variable, whilst age (both as continuous variable or proportion of patients aged > 70 years), cardiac aetiology of syncope, undetermined syncope, presence of heart diseases, no history of previous syncopal episodes, not full agreement with typical features of syncope along with vital and laboratory abnormalities were entered as covariates. Cardiogenic syncope, no history of previous syncopal episodes, not full agreement with typical features of syncope, abnormalities of vital and laboratory parameters were found to be

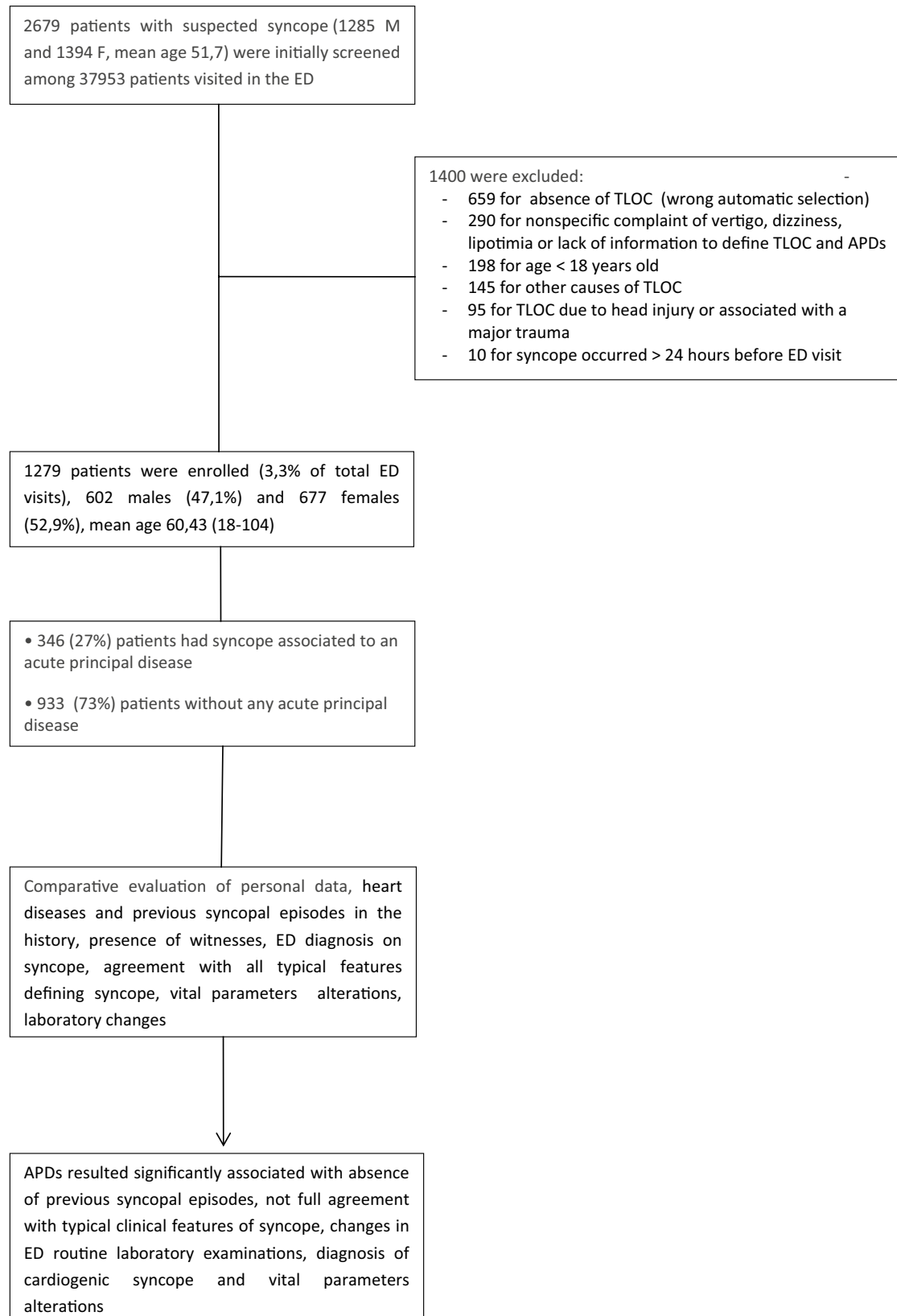


Fig. 1 Flow diagram of the study

Table 1 Characteristics of patients with and without an acute principal disease (APD)

Variable	Patients with APDs (<i>n</i> = 346)		Patients without APDs (<i>n</i> = 933)		<i>p</i> value
	<i>n</i>	95% CI	<i>N</i>	95% CI	
Age	68.6 (19.8)	66.5–70.7	57.2 (22.4)	55.8–58.6	<0.0001
Age > 70	204 (59)	53.7–64	331 (35.5)	32.5–38.7	<0.0001
Male gender	173 (50)	44.8–55.2	431 (46.2)	43–49.4	0,226
Heart diseases	74 (21.4)	17.4–26	112 (12)	10.1–14.2	<0.0001
Previous episodes	94 (27.2)	22.7–32.1	409 (43.8)	40.7–47	<0.0001
Witnesses	175 (50.6)	45.3–55.8	511 (54.8)	51.6–57.9	0,181
Cardiogenic syncope	58 (16.8)	13.2–21.1	38 (4.1)	3–5.5	<0.0001
Reflex syncope	65 (18.8)	14.8–23.3	505 (54.1)	50.9–57.4	<0.0001
Orthostatic syncope	112 (32.4)	27.4–37.6	196 (21)	18.4–23.8	<0.0001
Undetermined syncope	111(32.1)	27.4–37.2	194 (20.8)	18.3–23.5	<0.0001
Not full agreement with typical features	89 (25.7)	21.4–30.6	47 (5)	3.8–6.6	<0.0001
Vital parameters alterations	204 (59)	53.7–64	142 (15.2)	13.1–17.7	<0.0001
Laboratory changes	268 (78.6)	73.9–82.6	294 (34.2)	31.1–37.5	<0.0001
Admission	215 (62.1)	56.9–67.1	116 (12.4)	10.5–14.7	<0.0001

Age is presented as mean and standard deviation and as number and percentage of patients over 70 years; other categorical variables are presented as counts and percentages of patients

Table 2 Acute principal diseases detected

APD (<i>n</i> = 346)	<i>n</i>	%
Acute coronary syndrome	17	4.9
Other CV events	42	12.1
Acute neurological disorders	34	9.8
Haemorrhage or severe anemia	30	8.7
Other APD with pain, fluid loss or hypotension	82	23.7
Infectious disease	119	34.4
Major arrhythmias	22	6.4

Table 3 Binary logistic regression analysis of relationship between APDs and potential predictive factors

Variables	OR	95% CI	<i>p</i> value
Age	0.996	0.982–1.009	0.532
Age > 70 years	0.983	0.55–1.754	0.952
Cardiogenic syncope	2.882	1.619–5.131	<0.001
Undetermined syncope	1.453	0.994–2.123	0.054
Heart diseases	0.931	0.592–1.464	0.757
Absence of previous episodes	0.481	0.344–0.673	<0.001
Not full agreement with typical features	4.384	2.732–7.037	<0.001
Vital parameters alterations	6.293	4.542–8.719	<0.001
Laboratory abnormalities	4.447	3.142–6.292	<0.001

$R^2 = 0.440$ (Nagelkerke)

independently associated with the presence of APDs, whilst no significant associations could be observed with others factors.

Discussion

The main finding of this retrospective investigation is that syncope may be associated with APD in over a quarter of all patients (i.e., 27.1%). In the vast majority of cases these accounted for non-cardiovascular acute conditions (67%), mostly non-life-threatening, whilst severe acute cardiovascular conditions (e.g., acute coronary syndrome, pulmonary embolism, acute aortic syndrome, critical bradyarrhythmia, and ventricular tachycardia) were relatively less frequent (altogether accounting for ~15% of total APDs, corresponding to 4.2% of all patients enrolled), as previously reported in the literature [9].

Infectious diseases were the most frequently identified APDs in our population, and the actual association between these conditions and TLOC might encompass multiple factors such as hypotension due to dehydration, fever and hypoxia, or cough in case of pneumonia.

As concerns the leading factors reflecting the presence of syncope-associated APDs, our study confirms the important role of cardiogenic syncope. As already endorsed by the ESC guidelines [4], cardiac syncope is associated with high morbidity and mortality. Therefore, our data hence demonstrate that this increased risk may

be sometimes related to the presence of an APD, which is already identifiable at ED admission. In fact, more than half of our patients with cardiogenic syncope (58/96, i.e., 60.4%) were found to have an APD, being represented by acute coronary syndrome, major arrhythmias or other acute cardiovascular events (the most frequent were bradyarrhythmia and heart failure) in the vast majority of cases (i.e., up to 93%). Vital parameters abnormalities were also associated with APDs in our study population, and this is not surprising since these shall be regarded as clear signs of acute underlying conditions.

A medical history without previous syncopal episodes was found to be an additional predictive factor of APDs, a finding that shall be interpreted according to the evidence that recurrent syncope does not predict the risk of adverse outcomes [10], and is neither associated with the presence of structural heart disease [4]. A second peak of first-time incidence of syncope has been observed in the elderly, most likely attributable to age-related alterations of cardiovascular system and to other comorbidities, with high rate of underlying cardiac cause (of up to 34% of all cases) [4, 11]. A first episode of syncope in older patients shall hence be considered a sign of possible presence of APD. A syncope-associated APD could be identified in nearly half of all patients aged 70 years or older and without history of previous syncopal episodes in our cohort.

The fact that not the full agreement with typical features of syncope was associated with the presence of APDs is an intriguing evidence. In the case of acute neurological disorders, the frequent absence of these features could be due to the fact that TLOC could not have been always a real syncope. As concerns other APDs, atypical presentation could be explained by assuming that the mechanism causing the syncope is still active at the time of ED evaluation. This would suggest that while EPs are facing patients with TLOC after discriminating between syncopal TLOCs and different forms (as for the ESC guidelines), they shall also be able to promptly identify those with an atypical presentation of syncope, who do not fulfil typical clinical features (i.e., rapid onset, short duration, and spontaneous complete recovery). Priority shall thus be given to the identification of APD in the latter case, even before focusing on the underlying mechanism(s) of the syncope.

We finally found that some laboratory abnormalities were significantly associated with APD, and these notably displayed an excellent negative predictive value (NPV), as high as 88%. This confirms that patient management driven by results of some appropriate laboratory investigations may be clinically useful and safe, especially in patients with ambiguous or non-witnessed episodes [6, 7].

Limitation

Main limitations of this study are related to the monocentric and retrospective design; as concerns the second aspect, we disclose that retrospectively assessing an acute principal disease underlying a syncopal episode might be considered a subjective task.

Conclusion

This study shows that syncope is frequently associated with the presence of underlying APDs of varying severity, but mostly non-clinically threatening. This simple but straightforward finding has important relevance, since confirms that syncope is often to be considered as only a symptom of an underlying condition, not as a primary disease. In some cases, in fact, syncope is a direct expression of an active cardiovascular disease, through a reduction in the cardiac output (due to an arrhythmia, a structural heart or cardiopulmonary disease), or of a major haemorrhage, while, more frequently, is only an accompanying clinical feature during a different non-severe medical condition, characterized by pain, fluid loss or hypotension. In the absence of an acute disease, syncope should be attributed to a functional or structural impairment of the autonomic nervous system, causing orthostatic hypotension, or to a reflex mechanism. This observation confirms the appropriateness of the method suggested by the ESC guidelines, according to which EPs facing syncopal patients should first be engaged in the search for underlying diseases, especially those at risk of a rapid clinical deterioration; this first aim in the ED path will allow the timely identification of patients at highest risk of short-term adverse events and could reduce inappropriate hospitalizations and investigations, especially for hypotensive syncope caused by non-serious concomitant conditions. At this phase of patient management in the ED, accurate history taking (aimed at identifying previous syncopal episodes), detection of typical clinical features characterizing the syncope, along with abnormalities of routine laboratory investigations may have substantial relevance along with other prognostic factors, such a diagnosis of cardiogenic syncope and the presence of alterations of vital parameters. Further prospective studies would now be warranted to confirm the findings of our preliminary investigation.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s11739-021-02678-z>.

Acknowledgements No acknowledgment to be done

Author contribution FN takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed

interpretation, he conceived the study and designed the trial, managed the data and takes responsibility for the paper as whole; GM supervised the conduct of the trial and data collection and drafted the manuscript; IG and MB contributed to the conduct of the trial and data collection; GL provided statistical advice on study design and revised the paper for clarity; MM and GC revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

Funding No grant to be declared.

Data availability All data and materials as well as software application or custom code support their published claims and comply with field standards.

Compliance with ethical standard

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study received regulatory approval from the local ethical committee (Reference Number 0000749, 2/7/19).

Informed consent The study was carried out according to local legislation, with considerable organizational restrictions due to current pandemic.

References

1. Brignole M, Moya A, de Lange FJ et al (2018) ESC Scientific Document Group. 2018 ESC guidelines for the diagnosis and management of syncope. *Eur Heart J* 39(21):1883–1948
2. Brignole M (2018) Management of transient loss of consciousness in emergency department: what's new from 2018 European Society of Cardiology guidelines? *Emergency Care J* 14(7509):1–3
3. Moore AB, Su E, Weiss RE et al (2020) Frequency of abnormal and critical laboratory results in older patients presenting to the emergency department with syncope. *Acad Emerg Med* 27(2):161–164
4. Brignole M, Moya A, de Lange FJ et al (2018) ESC scientific document group practical instructions for the 2018 ESC guidelines for the diagnosis and management of syncope. *Eur Heart J* 39(21):e43–e80
5. Sheldon RS, Morillo CA, Krahn AD et al (2011) Standardized approaches to the investigation of syncope: Canadian Cardiovascular Society position paper. *Can J Cardiol* 27(2):246–253
6. Numeroso F, Mossini G, Lippi G, Cervellin G (2018) Analysis of temporal and causal relationship between syncope and 30-day events in a cohort of emergency department patients to identify the true rate of short-term outcomes. *J Emerg Med* 55(5):612–619
7. Quinn JV, Stiell IG, McDermott DA, Sellers KL, Kohn MA, Wells GA (2004) Derivation of the San Francisco Syncope rule to predict patients with short-term serious outcomes. *Ann Emerg Med* 43:224–232
8. General authorisation to process personal data for scientific research purposes. Italy's Official Journal no. 72, 26/03/12: 47–52
9. Brignole M, Alboni P, Benditt DG et al (2004) Guidelines on management (diagnosis and treatment) of syncope—update 2004. *Europace* 6(6):467–537
10. Chang AM, Hollander JE, Su E et al (2019) Recurrent syncope is not an independent risk predictor for future syncopal events or adverse outcomes. *Am J Emerg Med* 37(5):869–872
11. Grubb BP, Karabin B (2012) Syncope: evaluation and management in the geriatric patient. *Clin Geriatr Med* 28(4):717–728

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.