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Recurrent syncope is not an independent risk predictor for future syncopal events or adverse outcomes

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Abstract

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Conflicts of interest: Dr. Sun is a consultant for Medtronic.

Almost 20% of patients with syncope will experience another event. It is unknown whether recurrent syncope is a marker for a higher or lower risk etiology of syncope. The goal of this study is to determine whether older adults with recurrent syncope have a higher likelihood of 30-day serious clinical events than patients experiencing their first episode.

Methods: This study is a pre-specified secondary analysis of a multicenter prospective, observational study conducted at 11 emergency departments in the US. Adults 60 years or older who presented with syncope or near syncope were enrolled. The primary outcome was occurrence of 30-day serious outcome. The secondary outcome was 30-day serious cardiac arrhythmia. In multivariate analysis, we assessed whether prior syncope was an independent predictor of 30-day serious events.

Results: The study cohort included 3580 patients: 1281 (35.8%) had prior syncope and 2299 (64.2%) were presenting with first episode of syncope. 498 (13.9%) patients had 1 prior episode while 771 (21.5%) had more than 1 prior episode. Those with recurrent syncope were more likely to have congestive heart failure, coronary artery disease, previous diagnosis of arrhythmia, and an abnormal ECG. Overall, 657 (18.4%) of the cohort had a serious outcome by 30 days after index ED visit. In multivariate analysis, we found no significant difference in risk of events (adjusted odds ratio 1.09; 95% confidence interval 0.90–1.31; p=0.387).

Conclusion: In older adults with syncope, a prior history of syncope within the year does not increase the risk for serious 30-day events.

Trial registration number:

Introduction

Syncope, defined as a transient loss of consciousness and postural tone followed by complete, spontaneous return to neurological baseline,[1] is a common reason to visit the emergency department (ED), representing over 740,000 annual visits.[2] It is important to determine the etiology of syncope for multiple reasons, including prevention of adverse outcomes as well as quality of life issues. Unfortunately, up to 50% of patients will not have a diagnosis. Approximately 20% of patients with syncope will experience another syncopal event within two years.[1,3]

There are mixed data regarding the potential severity of illness of those with recurrent syncope. On the one hand, a negative evaluation during the first episode can suggest that patients with recurrence may be at lower risk of having a serious etiology, such as vasovagal syncope. Conversely, recurrences might portend a more serious etiology not discovered during a preliminary evaluation and might suggest the need for more detailed testing. Recurrent syncopal episodes have been associated with increased risk of fractures and lower quality of life,[4] but it is unknown if recurrence itself is a risk factor or may help identify the underlying cause.

The primary goal of this study was to determine whether older adults with recurrent syncope have a higher likelihood of 30-day serious events than patients experiencing their first episode of syncope.

Methods

We conducted a pre-specified secondary analysis of a large, multicenter, prospective cohort study to derive and validate a novel risk prediction model for 30-day death or serious cardiac outcomes in older adults with unexplained syncope (ClinicalTrials.gov identifier). The study was approved by the institutional review boards at all sites and written, informed consent was obtained from all participating subjects.

Eligible patients were ≥ 60 years of age with a complaint of syncope or near-syncope at 11 academic EDs across the United States. Exclusion criteria were as follows: intoxication, medical or electrical intervention to restore consciousness, inability or unwillingness to provide informed consent or follow-up information. Patients with a presumptive cause of loss of consciousness due to seizure, stroke or transient ischemic attack, or hypoglycemia were also excluded. The full study protocol has been published elsewhere.[5]

All patients underwent standardized history, physical examination, laboratory testing, and 12-lead ECG testing. Additional testing and patient disposition were directed by the treating clinical providers. We conducted 30-day patient follow-up using previously described methods,[6] including a review of the electronic medical records by local research personnel to evaluate for serious outcomes within 30 days from the index ED evaluation. Additionally, we called enrolled patients at 30 days to identify out-of-hospital deaths, ED visits, and hospitalizations that occurred outside of the study sites.

Data variables collected were consistent with reporting guidelines for ED based syncope research (table 1).[7] We collected data on comorbid factors such as a history of syncope. Data on current medications were organized by class of drug and included beta-blockers, calcium channel blockers, and other antiarrhythmic agents (e.g., amiodarone). Heart murmur on examination was marked as present, absent, or not assessed. ECG interpretations were based on the first ECG obtained in the ED and were abstracted by one of five research study physicians who were blinded to all clinical data.

Recurrent syncope was defined by patient report of one or more episodes(s) of syncope in the past year. An answer of “don’t recall” was categorized as no prior episode.

The primary outcome was a composite endpoint of a serious clinical outcome, which is defined as any of the following: a significant arrhythmia (ventricular fibrillation, symptomatic ventricular tachycardia longer than 30 seconds, sick sinus syndrome, sinus pause longer than 30 seconds, Mobitz II heart block, complete heart block, symptomatic supraventricular tachycardia, or symptomatic bradycardia <40 beats per minute),[8] myocardial infarction, cardiac intervention, new diagnosis of structural heart disease, stroke, pulmonary embolism, aortic dissection, subarachnoid hemorrhage, cardiopulmonary resuscitation, internal hemorrhage/anemia requiring transfusion, recurrent syncope/fall resulting in major traumatic injury, and death within 30 days. Our secondary outcome evaluated only 30 day cardiac arrhythmias as cardiac causes of syncope increases with age.[9,10]

Data analyses were performed using the R package (R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/).Patient characteristics are described as number and percentage or mean and SD. Differences between categorical variables are analyzed with a chi-square test or Fisher's exact test and differences between continuous variables with two sample t-tests. Significance was defined as $p<0.05$, and the results of the multivariate logistic regression model are presented as adjusted ORs with 95% CIs. Our primary analysis compared those with prior syncope to those without in an adjusted logistic regression, with gender, race, history of congestive heart failure, history of coronary artery disease, history of arrhythmia, abnormal ECG, dyspnea, hypotension, and physician risk assessment in the models.

Results:

There were 6930 eligible subjects and 3686 (53.1%) of these consented and enrolled in the study. Of those consented and enrolled, 3580 subjects had complete follow up and information on recurrent syncope data (Figure 1). Of these, 2299 (64.2%) did not have any prior episodes, 498 (13.9%) subjects had 1 prior episode while 771 (21.5%) had more than 1 prior episode within the past year. Subjects had a mean age of 72.8 ± 9.0 years old, 1848 (51.6%) were male, and 2973 (83.5%) were white. Overall 1281 (35.8%) reported a history of a prior syncopal event. Compared to patients without prior syncope, patients with prior syncope had more comorbidities, and symptoms of dyspnea, hypotension, and an abnormal ECG8 compared to those without a prior syncopal event (Table 1).

Overall, there were 657(18.4%) significant events at 30 days, 266 (20.8%) in those with prior syncope and 391 (17.0%) in those without (p=0.005); 30 day death occurred in 44 patients (1.2%) (Table 2). In univariate testing, recurrent syncope was a predictor of 30 day serious outcomes (unadjusted OR, 1.28, 95% CI 1.07–1.52). However, in multivariable modeling after adjusting for confounders, recurrent syncope was not an independent predictor of 30 day serious outcomes (adjusted OR 1.09, 95% CI 0.90–1.31) (Table 2). In secondary analysis, there were 307 (8.6%) serious cardiac arrhythmias. Compared to those without previous syncope, patients with recurrent syncope were more likely to have a serious event (unadjusted odds ratio 1.50, 95% CI 1.18–1.90). After adjusting for confounders, we found there was no association of recurrent syncope for serious cardiac arrhythmias (aOR 1.29, 95% CI 0.99–1.66) (Table 3). When stratifying by number of recurrent syncope episodes (either one previous episode, or more than 1 previous episode) in multivariate analysis, there was no association with 30 day serious outcomes (supplementary table). However, there was an association of serious cardiac arrhythmias with a single recurrent syncopal episode (supplemental tables).

Discussion:

In this cohort of older patients with syncope in the emergency department, we found that over 30% of the population reported having one or more syncopal events in the preceding year. This is higher than previous evaluations of syncope, which has been estimated between 2 to 20% over a lifetime.[9,12,13] This may be due to the older age of our population. The risk of adverse cardiovascular events was higher in those with a previous reported history of

syncope. However, after adjusting for other risk factors, this increased risk was attenuated. Thus, isolated history of syncope should not be considered an independent risk factor; rather, a patients' risk of cardiovascular disease should be the most important part of the assessment. However, it is critical to note that although the predictive value of recurrent syncope may not be independently predictive, when used in clinical practice, it still serves as a marker of a poor prognosis (even if it can be explained by other risk factors).

There is conflicting literature on the significance of recurrent syncope. Previous literature has shown that the most common cause of syncope is vasovagal, which is mostly benign but presents at a younger age.[14] Older patients may not be as straightforward. Chen et al. evaluated patients referred to an electrophysiology service for syncope and found that older patients often were more likely to have multiple causes of their syncope.[15] Bennett et al. include risk factors for high risk syncope as those over the age of 60 with previous cardiac history.[9] Sheldon et al. found that older patients were more likely to have cardiac causes of syncope, including complete heart block, SVT, and VT with a median of two syncopal spells.[10] Longitudinal studies show that those with recurrent syncope tends to have worse prognosis. One recent paper found that in 27 of 110 patients with prior syncope had a diagnostic event within a 4 week monitoring period upon repeat presentation.[16] Ruwald et al. evaluated recurrent syncope patients in a Danish registry and found that recurrent syncope was associated with a 3.2-fold increased risk in 30-day and 1-year mortality compared to first time syncope.[13]

These data are in contrast with prior emergency department-based studies, which may be a different population of undifferentiated syncope. Numeroso et al. evaluated 347 patients with syncope of undetermined origin and found that almost half of patients determined to have intermediate or high risk syncopal criteria had previous episodes, yet recurrent syncope was not an independent predictor of adverse events.[17] In the derivation cohort of the San Francisco syncope rule, 16.5% of patients with a serious outcome had a history of syncope versus 18.3% of those without a serious outcome, and the group did not find that it was an independent predictor of adverse events.[18] Grossman et al. conducted a decision rule that incorporated "multiple syncopal episodes within the last 6 months" as a risk factor for adverse events, but only found it in 6% of those with a serious outcome had a history of recurrent syncope versus 14% in those without a serious outcome.

There are some limitations that must be acknowledged. Despite rigorous methodology, we cannot be sure that we detected all serious cardiac events that occurred. However, the definition of serious cardiac arrhythmia included arrhythmias that were symptomatic making it likely that these patients would have come to medical attention. The study was a convenience sample of patients and thus sampling bias may occur, and the incidence of both recurrent syncope and serious cardiac arrhythmia in our study may be different than actual practice. We did not use an adjudicated definition of recurrent syncope but rather relied on patient self-report without confirmation and detailed record review; however this mirrors what is done in clinical practice. Thus it might be seen as a methodological weakness or enhancing generalizability.

In older adults presenting to the ED with syncope, a prior history of syncope does not increase the risk for adverse 30-day events, and should not be considered an independent risk factor, but perhaps another sign for those with cardiovascular risk factors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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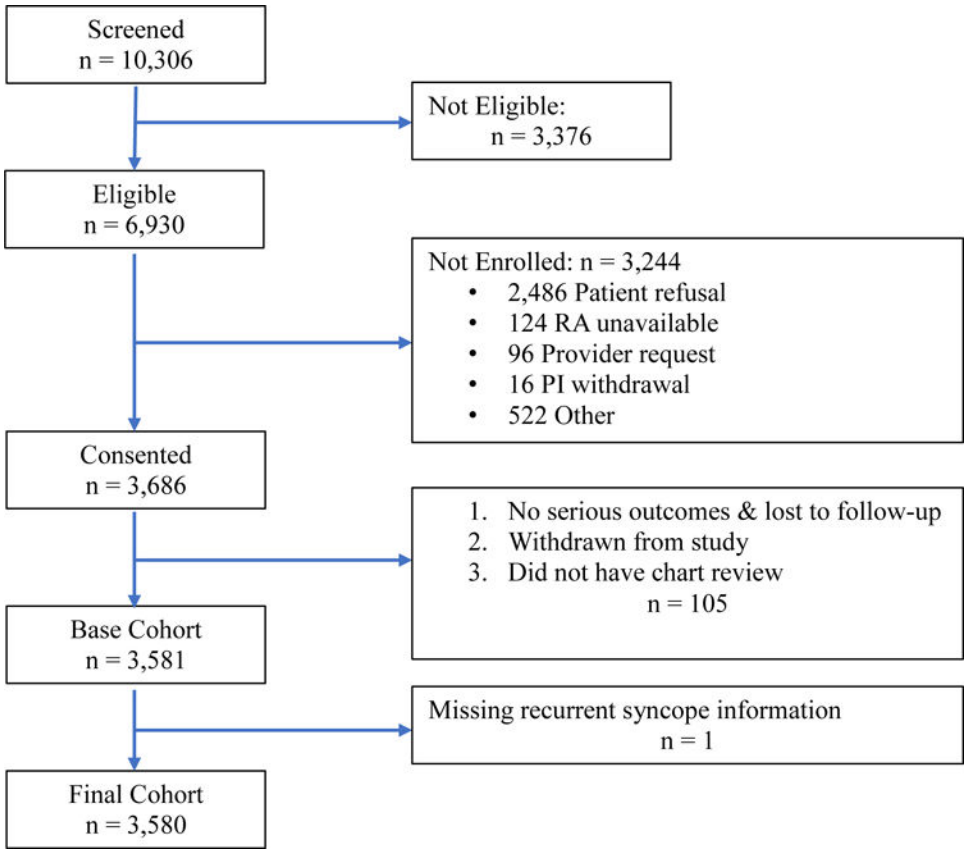

Figure 1.
CONSORT diagram

Table 1.

Study Cohort Characteristics

Demographic variables	Overall cohort	No prior episodes	Recurrent syncope	P value
	N=3580	N=2299	N=1281	
	N (%)	N (%)	N (%)	
Age, mean (SD)	72.8 (9.0)	72.8 (9.0)	72.7 (9.0)	0.766
Age				0.751
60 to <70	1539 (43.0)	997 (43.4)	542 (42.3)	
70 to <80	1155 (32.3)	727 (31.6)	428 (33.4)	
80 to <90	729 (20.4)	473 (20.6)	256 (20.0)	
90+	157 (4.4)	102 (4.4)	55 (4.3)	
Length of Stay (hours)				
Admitted, mean (SD)	96.8 (110.4)	95.84 (125.20)	98.29 (84.40)	0.685
Observed, mean (SD)	36.5 (38.6)	34.43 (34.51)	40.74 (45.58)	0.005
Discharged, mean (SD)	9.4 (40.0)	8.96 (33.50)	10.26 (51.29)	0.687
Gender				0.820
Female	1732 (48.4)	1109 (48.2)	623 (48.6)	
Male	1848 (51.6)	1190 (51.8)	658 (51.4)	
Race				0.778
White or Caucasian	2973 (83.5)	1909 (83.7)	1064 (83.2)	
Black or African American	478 (13.4)	305 (13.4)	173 (13.5)	
Asian	41 (1.2)	27 (1.2)	14 (1.1)	
Other	67 (1.9)	39 (1.7)	28 (2.2)	
Co-Morbidities				
Congestive Heart Failure	449 (12.5)	251 (10.9)	198 (15.5)	<0.001
Coronary Artery Disease	979 (27.4)	592 (25.8)	387 (30.3)	0.004
Arrhythmia	802 (22.4)	471 (20.5)	331 (25.9)	<0.001
Dyspnea	747 (21.4)	417 (18.6)	330 (26.3)	<0.001
Hypotension	382 (10.7)	207 (9.0)	175 (13.7)	<0.001
Abnormal ECG	1948 (55.4)	1206 (53.4)	742 (59.0)	0.001
Physician Risk Assessment, mean (SD)	9.2 (13.2)	8.8 (12.5)	9.8 (14.3)	0.027

Abnormal ECG includes: any non sinus rhythm, left ventricular hypertrophy, bundle branch blocks, or interval prolongation

Table 2:

Unadjusted and adjusted regression models predicting 30 day serious outcomes

	Unadjusted OR	95% CI	Adjusted OR	95% CI
Recurrent Syncope	**1.28**	**(1.07, 1.52)**	1.09	(0.90, 1.31)
Gender (male)	**1.41**	**(1.19, 1.68)**	1.20	(0.99, 1.45)
Race (not White)	**0.72**	**(0.56, 0.91)**	**0.74**	**(0.57, 0.97)**
History of Congestive Heart Failure	**2.06**	**(1.65, 2.58)**	**1.37**	**(1.05, 1.77)**
History of Coronary Artery Disease	**1.53**	**(1.28, 1.84)**	0.99	(0.80, 1.22)
History of Arrhythmia	**2.61**	**(2.17, 3.13)**	**2.04**	**(1.66, 2.49)**
Abnormal ECG	**2.27**	**(1.89, 2.74)**	**1.75**	**(1.42, 2.15)**
Dyspnea	**1.81**	**(1.49, 2.20)**	**1.76**	**(1.43, 2.16)**
Physician Risk Assessment	**1.03**	**(1.02, 1.04)**	**1.03**	**(1.02, 1.03)**
Hypotension	**1.85**	**(1.44, 2.34)**	**1.64**	**(1.25, 2.13)**

Serious outcome defined as any: significant arrhythmia (ventricular fibrillation, symptomatic ventricular tachycardia longer than 30 seconds, sick sinus syndrome, sinus pause longer than 30 seconds, Mobitz II heart block, complete heart block, symptomatic supraventricular tachycardia, or symptomatic bradycardia <40 beats per minute), myocardial infarction, cardiac intervention, new diagnosis of structural heart disease, stroke, pulmonary embolism, aortic dissection, subarachnoid hemorrhage, cardiopulmonary resuscitation, internal hemorrhage/anemia requiring transfusion, recurrent syncope/fall resulting in major traumatic injury, and death within 30 days

Table 3:

Unadjusted and adjusted regression models predicting 30 day cardiac arrhythmias

	Unadjusted OR	95% CI	Adjusted OR	95% CI
Recurrent Syncope	**1.50**	**(1.18, 1.90)**	1.29	(0.99, 1.66)
Gender (male)	**1.31**	**(1.03, 1.66)**	1.08	(0.83, 1.39)
Race (not White)	**0.55**	**(0.37, 0.79)**	**0.65**	**(0.43, 0.97)**
History of Congestive Heart Failure	**2.16**	**(1.60, 2.87)**	1.10	(0.79, 1.52)
History of Arrhythmia	**6.32**	**(4.96, 8.08)**	**4.68**	**(3.60, 6.09)**
Abnormal ECG	**3.53**	**(2.66, 4.77)**	**2.32**	**(1.71, 3.21)**
Dyspnea	**1.49**	**(1.13, 1.93)**	**1.41**	**(1.05, 1.87)**
Physician Risk Assessment	**1.02**	**(1.02, 1.03)**	**1.02**	**(1.01, 1.02)**
Hypotension	**1.54**	**(1.09, 2.13)**	**1.30**	**(0.89, 1.86)**