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ORIGINAL RESEARCH

Clinical Associations of Injuries Caused by Vasovagal Syncope: A Cohort Study From a Tertiary Syncope Unit

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BACKGROUND: Recent research has revealed that vasovagal syncope (VVS) leads to a high incidence of injuries; however, clinical associations of injury are not well-established. We present data from an ongoing VVS cohort and aimed to determine characteristics associated with VVS-related injury.

METHODS AND RESULTS: Between 2017 and 2020, consecutive patients ≥18 years of age presenting to a tertiary syncope unit and diagnosed with VVS were included. Clinical characteristics relevant to syncope were obtained for the index episode. The outcome was incidence of injury during VVS, documented by clinical evaluation at the syncope clinic. Among 1115 patients (mean age, 45.9 years; 48% women), 260 injuries (23%) occurred. History of VVS-related injuries (adjusted relative risk [aRR], 1.80 [95% CI, 1.42–2.29]), standing position (aRR, 1.34 [95% CI, 1.06–1.68]), and female sex (aRR, 1.30 [95% CI, 1.06–1.60]) were associated with injury, whereas recurrent VVS (aRR, 0.63 [95% CI, 0.49–0.81]) and syncope in the noon/afternoon (aRR, 0.70 [95% CI, 0.56–0.87]) and evening/night (aRR, 0.43 [95% CI, 0.33–0.57]) compared with morning hours were associated with lower risk. There was a trend for higher rates of injury with overweight/obesity (aRR, 1.23 [95% CI, 0.99–1.54]) and syncope occurring at home (aRR, 1.22 [95% CI, 0.98–1.51]). In a per-syncope analysis considering up to 3 previous episodes (n=2518, 36% traumatic), syncope at home (aRR, 1.33 [95% CI, 1.17–1.51]) and absence of prodromes (aRR, 1.34 [95% CI, 1.09–1.61]) were associated with injury.

CONCLUSIONS: Patient characteristics, VVS presentations, the circumstances, and surroundings can determine the risk of injury. These associations of VVS-related injury identify at-risk individuals and high-risk situations. Future prospective studies are needed to investigate potential strategies for prevention of post-VVS injury in recurrent cases.

Key Words: injuries ■ physical injury ■ syncope ■ trauma ■ vasovagal syncope-related injury ■ vasovagal syncope ■ wounds

Vasovagal syncope (VVS) manifests as a transient loss of consciousness (TLOC) with loss of postural tone as a result of reduced cerebral blood flow.[1] The lifetime prevalence of VVS is 40% among adults, and it is the cause 1% to 1.5% of emergency department visits in the United States.[2] VVS is characterized by a spontaneous and rapid recovery, is not associated with an increased risk of adverse outcomes, and does not indicate an underlying cardiovascular disease in most circumstances; therefore, it is often considered a benign condition.[3] However, it has been demonstrated that recurrent VVS can significantly reduce quality of life,[4] and an episode of TLOC portends the risk of falling and traumatic injury.

Recent evidence indicates that patients who present to the hospital with syncope have an 80% higher risk of injury in the following year compared with controls.[5] A 2021 meta-analysis of 23 studies involving 3593 patients diagnosed with VVS found that 33.5% of individuals

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CLINICAL PERSPECTIVE

What Is New?

- Among 1115 adults presenting with an episode of vasovagal syncope to the syncope unit, 23% reported injury, and 3% had severe injuries; moreover, in 2518 vasovagal syncope episodes, 36% were associated with injury.
- History of syncope-associated injuries, experiencing a first-time episode, and syncope in the morning or while standing were associated with a higher risk of injury.
- Female sex, overweight and obesity, having syncope at home, and absence of prodromal symptoms indicated a higher likelihood of trauma.

What Are the Clinical Implications?

- Patient characteristics, VVS presentations, and perisyncopal circumstances affect the risk of injury and should be considered for implementing preventive measures.
- Patients with recurrent VVS should be educated about the risk of injury and how to minimize this risk.

Nonstandard Abbreviations and Acronyms

aRR	adjusted relative risk
POST	Prevention of Syncope Trials
TLOC	transient loss of consciousness
VVS	vasovagal syncope

reported a history of traumatic syncopal episodes.[6] These observations signify the importance of injury as a clinical outcome in VVS, but despite this importance, there is a paucity of data about predictors and risk factors of VVS-related injuries. Identification of clinical associations of injury is a crucial step in improving management of VVS and should prompt future research to not only focus on strategies to prevent recurrences but also to find approaches to reduce the risk of injury if VVS occurs.

Herein, we present data from an ongoing cohort of patients with VVS from a tertiary syncope unit, with the aim of investigating clinical associations of injury during VVS episodes.

METHODS

Transparency and Openness Promotion

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Design and Population

The current analysis was performed on data from the ongoing cohort study of patients with VVS at the Syncope Unit of Tehran Heart Center[7] and includes adults >18 years of age who received a diagnosis of VVS between December 2017 and November 2020. This study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional committee for ethics in biomedical research (ID: IR.TUMS.SPH.REC.1399.152). All participants provided written informed consent for use of their anonymized information in aggregate form in future studies.

VVS was diagnosed based on clinical history provided by patients, families, and bystanders who witnessed the syncopal event, along with physical examination, according to the latest syncope guidelines.[8,9] After confirming TLOC and syncope as its cause, the diagnosis of VVS was made by the treating physician if features compatible with VVS were recognized.[8,9] In uncertain cases, VVS was only diagnosed after exclusion of other potential causes of syncope. Diagnosis of VVS was not based on tilt testing. Exclusion criteria were evidence of orthostatic hypotension or postural orthostatic tachycardia, defined as a decrease in blood pressure ≥20/10 mm Hg or an increase in heart rate ≥30 bpm after a 5-minute stand test, ventricular pause longer than 3 seconds, or a fall in blood pressure >50 mm Hg after carotid sinus massage in patients >40 years of age who had an uncertain diagnosis, an ejection fraction ≤40%, and presence of severe valvular disease in echocardiography. Repeat visits at the syncope clinic were not included.

Patient- and Episode-Related Variables

Patients were interviewed at the syncope unit about clinical characteristics of their symptoms, and the conditions before, during, and after their most recent syncopal episode that prompted presentation to the syncope unit. The most recent VVS spell is hereinafter referred to as the index episode. In patients with history of prior VVS spells, clinical characteristics of up to 2 previous episodes were obtained in addition to the index episode.

The study questionnaire consisted of past medical history, family history of syncope, the time and location of VVS occurrence, identifiable triggers, prodromal symptoms, patient's position at the time of VVS, and specific symptoms during syncope and after recovery. The time of syncope during the day was categorized into morning (waking up until 11:59 AM), noon/afternoon (12:00 PM–17:59 PM), and evening/night (after 18:00 PM). Specific triggers including injections/blood draw, emotional stress, medical/dental setting, pain, exposure to hot water, and crowded/warm places were considered. Prodromes were defined as symptoms experienced

immediately before loss of consciousness and not symptoms during presyncopal episodes. History of diabetes, hypertension, and anemia were based on patient self-report. Participants who reported a diagnosis of syncope in first-degree relatives were considered to have a family history of syncope. Overweight or obesity were defined as a body mass index of ≥25 kg/m^2.

Outcome

The outcome of interest was the incidence of injury during the index VVS episode. Injuries were clinically evaluated at the syncope clinic, and evidence of bruising, abrasion, laceration, head injury, musculoskeletal pain, or fractures that had occurred during VVS were considered as the outcome. Injury severity was considered as mild (bruising, abrasion), moderate (musculoskeletal pain, laceration, or mild injury to the head, when neither had prompted an emergency visit), and severe (fractures, laceration, musculoskeletal pain, or head injury that needed an emergency department visit, or head injury associated with concussion or posttraumatic amnesia).

The primary per-patient analysis included all index syncopal events that occurred just before presentation to syncope clinic. In cases of previous attacks, history of syncope-related injury was also obtained for a maximum of 2 prior syncopal episodes, in a retrospective approach based on clinical records and patient self-report. Additionally, in a per-syncope analysis, data for up to 3 VVS episodes (the index episode plus up to 2 prior events) were combined, and the frequency of injury and its associations with clinical characteristics were investigated. The variables used in the per-syncope approach were specific to each episode.

Statistical Analysis

Categorical variables are represented as number (percentages) and were tested by Pearson χ^2 test. The distribution of age was assessed by inspection of histogram and Q-Q plots. To obtain better estimates of effect size, relative risk (RR) was chosen over odds ratio because the rate of outcome was high (>10%).[10] Incidence risks for injury and RR with corresponding 95% CIs were calculated according to 2-by-2 tables of exposure and outcome (injury) using the Wald interval. Univariate RRs and 95% CIs for age were calculated by applying log-binomial regression per 10-year increments of age.

For multivariable analysis, the log-binomial regression model was used to acquire adjusted RR (aRR) and 95% CI.[10] A full multivariable model with all potential explanatory variables was used, because the study aimed to identify clinical associations of injury. To determine the factors most strongly associated with injury and their discriminatory power, another multivariable model was developed. Candidate variables associated with injury with $P<0.1$ in univariate and multivariable analysis were used. Variables were dropped if they had high correlation with other predictors in the model. The final model was selected based on the highest area under the curve. In the per-syncope analysis, a generalized estimating equation log-binomial model with an exchangeable correlation structure was used to account for multiple (up to 3) syncopal episodes in the same patient. All analyses were performed using R (version 4.0.2; R Foundation for Statistical Computing) and R studio (version 1.3.1073).

RESULTS

Overall, 1362 patients with a working diagnosis of VVS were screened. After applying eligibility criteria, 143 individuals <18 years of age, 19 cases with evidence of orthostatic hypotension/postural tachycardia, 63 patients with evidence of carotid sinus hypersensitivity, and 22 patients who did not consent to participation were excluded, and 1115 individuals were investigated in this analysis. The study population had a mean age of 45.9 years and included 535 (48%) women. The median number of lifetime syncopal episodes was 3, and the median for previous year episodes was 2.

In 460 patients (41%), a specific trigger for VVS was identified. Among this group, the most common factor inducing VVS was being in a crowded/warm place in 180 patients (39%). Other patients with known triggers reported to have experienced syncope resulting from exposure to hot water (23%), injections/blood draw (20%), pain (16%), emotional stress (16%), or undergoing a medical/dental procedure (9%). Most participants (82%) reported prodromal symptoms before their episodes. Such symptoms involved dizziness (68%), blurred vision (56%), palpitations (35%), diaphoresis (35%), nausea (32%), heat feeling (27%), flushing (11%), abdominal discomfort (10%), or aura (5%). Forty-four patients (4%) had visited the emergency department because of syncope before presentation at the syncope unit.

Per-Patient Analysis

Among index syncopal episodes evaluated at the syncope clinic, 260 (23%) had resulted in physical injury. In univariate analysis, patients who experienced syncope in the morning ($P<0.001$), at home ($P<0.001$), or while standing ($P<0.001$) had a higher risk for injury. Syncope without specific triggers ($P=0.009$) and without prodromal symptoms ($P=0.018$) also showed a higher propensity to cause injury. Moreover, overweight or obesity ($P=0.021$), or a previous history of injury during VVS ($P<0.001$), were associated with higher risk, as detailed in Table 1. Female patients had a 23% higher risk of

injuries compared with male patients, but this association did not reach statistical significance (*P*=0.060).

In the multivariable adjusted model, female sex (*P*=0.012), syncope during morning hours (as compared with noon/afternoon [*P*=0.001] and evening/night [*P*<0.001]), and standing position (*P*=0.012) were significantly associated with injury (Table 1). History of syncope-related injury remained strongly associated with an 80% higher relative risk of being injured again (*P*<0.001). Moreover, patients who experienced recurrence of VVS had a lower number of traumatic incidents compared with those who had VVS for the first time (*P*<0.001). It is important to note that this result was about the most recent episode of VVS just before the clinic visit. Conversely, any history of syncope-related injury (and not injury in the most recent episode) was present in 307 (38%) patients with recurrent episodes, compared with 79 (26%) patients with first-time VVS (*P*<0.001). That is, a higher likelihood of injury was observed because of a higher frequency of episodes, but a patient with recurrent VVS was less likely to have an injury in subsequent attacks.

There was a nonsignificant trend between VVS at home and injury in the adjusted model (aRR, 1.21 [95% CI, 0.98–1.50]; *P*=0.080). The same applied to association of injury risk with overweight/obesity (*P*=0.074), absence of specific triggers (*P*=0.061), and presence of family history in first-degree relatives (*P*=0.075; Table 1). Notably, older age and syncope in the absence of prodromes did not indicate a higher risk.

A total of 8 categorical variables (previous syncope-related injury, time and location of syncope, prodromes, standing position, first-time occurrence, sex, and overweight/obesity) were selected for the predictive multivariable model (area under the curve, 0.70 [95% CI, 0.66–0.73]). Patients with ≤1 predictor had a low risk of injury, whereas presence of more predictors demonstrated a higher probability of injury (Figure 1; Table S1).

Injury Severity

Among 260 patients who suffered injury, 161 (62%) events were mild, 67 (26%) were moderate, and 32 (12%) were severe (Figure 2). The risk of moderate to severe injury was higher in patients with history of previous VVS-related injury (*P*=0.001). Conversely, the presence of prominent prodromes (*P*=0.005) and syncope during evening/night compared with morning hours (*P*=0.001) were associated with lower moderate-to-severe injury risk. There were trends indicating associations between female sex with higher risk (*P*=0.031) and recurrent VVS with lower risk of moderate-to-severe injury (*P*=0.052). Results are presented in detail in Table 2.

Among all injuries, presence of prodromes was associated with a lower likelihood of moderate-to-severe injury compared with mild injury (*P*=0.006). No other association was identified with severe or moderate-to-severe injury (Table S2).

Per-Syncope Analysis

Within the study population, 305 (27%) had experienced VVS for the first time, 217 (20%) had history of 2 episodes, and 593 (53%) reported a history of ≥3 syncopal attacks during their lifetime. Up to 3 episodes were included for each patient, accounting for a total of 2518 syncopal episodes considered in the per-syncope analysis. Among these, 2001 (80%) had occurred in the preceding year.

In 909 (36%) syncopal episodes, TLOC resulted in injury. In both univariate and multivariable analysis, experiencing VVS episodes during evening/night was associated with a lower injury risk when compared with morning hours, and syncope at home showed a significant association with injury (Table 3). As expected, syncope at the time of standing resulted in a higher number of injuries. Presence of prodromes was associated with a 25% lower relative risk compared with syncope without prodromes in the adjusted model and, unlike the per-patient analysis, reached statistical significance (*P*=0.003). Episodes with known triggers were associated with fewer injuries in the univariate analysis; however, this association was not observed after adjustment (*P*=0.889). Although there was a trend toward higher risk of injury in older participants, the adjusted model did not verify this association (*P*=0.513). Table 3 demonstrates RRs and aRRs for investigated characteristics.

DISCUSSION

In this cohort of patients with VVS who presented to a tertiary syncope unit, we found a high prevalence of injury, 23% of the most recent attacks and 36% of recent prior episodes. Only 3% of patients presented with severe injuries. The results demonstrated characteristics strongly associated with injury, such as experiencing attacks in the morning or while standing, previous injury during syncope, and a first incidence of VVS. Moreover, having VVS at home, absence of prodromes, overweight/obesity, and female sex were characteristics highly suggestive of injury risk that did not consistently meet statistical significance. Figure 3 presents an illustrated summary of these findings. The associations had a fair, but not optimal, predictive power for injury, indicating the need for further research on this subject.

A notable finding was the higher predisposition to injury when syncope occurred earlier in the day, specifically in the morning. Univariate results in Tables 1 and 3 showed a higher risk during noon/afternoon

Table 1. Characteristics Associated With Vasovagal Syncope-Related Injury per Patients

Characteristic	All, n=1115	With injury, n=260	Injury risk (95% CI)	Univariate		Multivariable	
				Relative risk (95% CI)	*P* value	Adjusted relative risk (95% CI)	*P* value
Age, y	45.9±17.3	46.8±17.4	…	1.04 (0.98–1.10) *	0.245	1.01 (0.94–1.07)*	0.864
Sex							
Men	580	122	0.21 (0.18–0.25)				
Women	535	138	0.26 (0.22–0.30)	1.23 (0.99–1.52)	0.060	1.30 (1.06–1.60)	0.012
BMI, kg/m^2							
<25	472	94	0.20 (0.16–0.24)				
≥25	643	166	0.26 (0.22–0.29)	1.30 (1.04–1.62)	0.021	1.22 (0.98–1.53)	0.074
Recurrent syncope							
First time	305	78	0.26 (0.21–0.31)				
Recurrent	810	182	0.22 (0.20–0.26)	0.88 (0.70–1.11)	0.274	0.63 (0.49–0.81)	<0.001
Previous injury after syncope							
No	919	190	0.21 (0.18–0.23)				
Yes	196	70	0.36 (0.29–0.43)	1.73 (1.38–2.17)	<0.001	1.80 (1.42–2.29)	<0.001
Diabetes							
Absent	1049	243	0.23 (0.21–0.26)				
Present	66	17	0.26 (0.16–0.38)	1.11 (0.73–1.70)	0.629	0.99 (0.63–1.54)	0.954
Hypertension							
Absent	862	197	0.23 (0.20–0.26)				
Present	253	63	0.25 (0.20–0.31)	1.09 (0.85–1.39)	0.498	0.99 (0.76–1.30)	0.952
Anemia							
Absent	918	215	0.23 (0.21–0.26)				
Present	197	45	0.23 (0.17–0.29)	0.98 (0.74–1.29)	0.862	0.93 (0.72–1.21)	0.602
Family history of syncope							
Absent	1016	230	0.23 (0.20–0.25)				
Present	99	30	0.30 (0.21–0.4)	1.34 (0.97–1.84)	0.085	1.29 (0.97–1.70)	0.075
Syncopal episode time							
Morning	289	103	0.36 (0.3–0.41)	Reference		Reference	
Noon/afternoon	410	100	0.24 (0.2–0.29)	0.68 (0.54–0.86)	0.001	0.70 (0.56–0.87)	0.001
Evening/night	416	57	0.14 (0.11–0.17)	0.38 (0.29–0.51)	<0.001	0.43 (0.33–0.57)	<0.001
Syncope occurred at							
Outside home	540	99	0.18 (0.15–0.22)				
Home	575	161	0.28 (0.24–0.32)	1.53 (1.22–1.91)	<0.001	1.21 (0.98–1.50)	0.080
Specific identifiable triggers							
Absent	655	171	0.26 (0.23–0.3)				
Present	460	89	0.19 (0.16–0.23)	0.74 (0.59–0.93)	0.009	0.81 (0.65–1.01)	0.061
Prodromes							
Absent	202	60	0.30 (0.23–0.37)				
Present	913	200	0.22 (0.19–0.25)	0.74 (0.58–0.94)	0.018	0.87 (0.68–1.10)	0.231
Position before syncope							
Sitting or recumbent	440	75	0.17 (0.14–0.21)				
Standing	675	185	0.27 (0.24–0.31)	1.61 (1.26–2.04)	<0.001	1.34 (1.07–1.69)	0.012

Age is represented as mean±SD. BMI indicates body mass index.
*Relative risks are calculated per 10-year increments for age.

versus evening/night hours; however, this association was not statistically significant in the adjusted models, because the confidence intervals marginally overlapped. As shown in Tables 2 and 3, syncope in the morning was associated with traumatic injury compared with evening/night, but the difference between

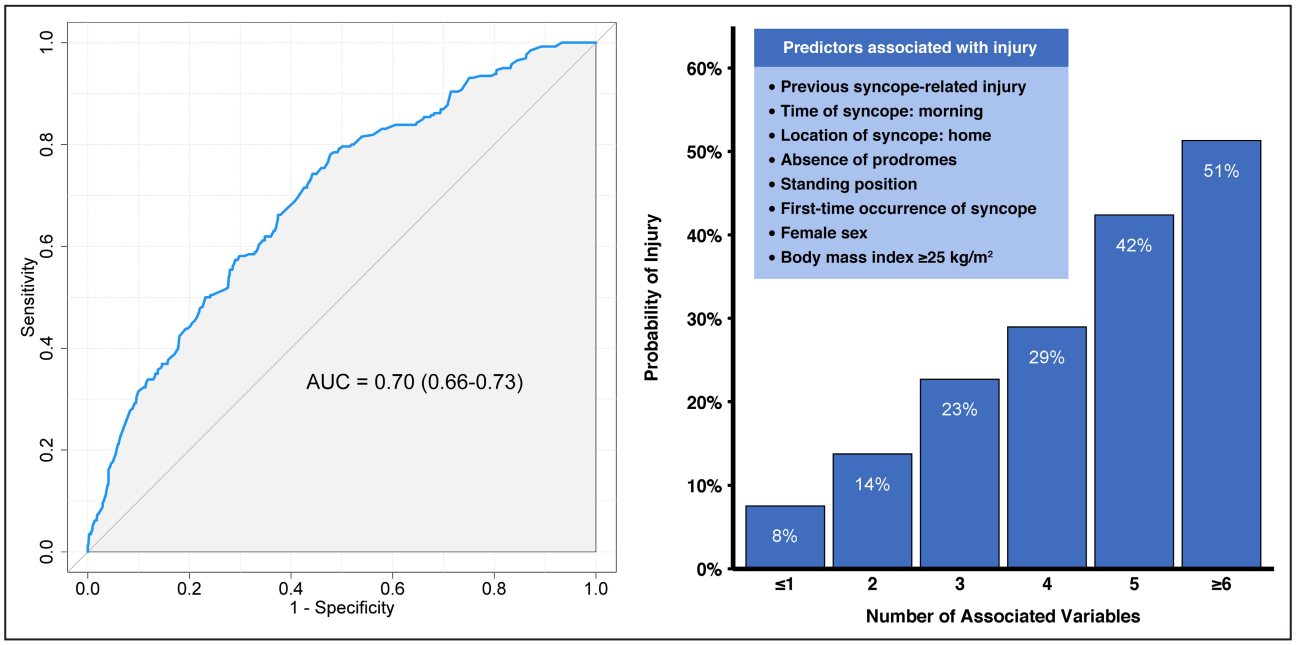


Figure 1. The predictive multivariable model developed based on 8 variables associated with injury.
AUC indicates area under the curve.

morning and noon/afternoon did not meet statistical significance. The role of circadian rhythm in autonomic activity and its effects on hemodynamic parameters might be relevant. In a study of 12 healthy subjects, Hu et al have shown that tilt-test-induced presyncope was more likely during biological night (10:30 PM to 10:30 AM) and that participants experienced more severe prodromal symptoms during the night.[11] However, the association of injury with the circadian rhythm has not been studied. It can be hypothesized that prolonged fasting and recumbent position during the night may result in an accelerated initiation of VVS with less severe prodromes, giving patients less time to avoid injury if falling occurs. Nevertheless, this finding indicates an area for future investigations.

Susceptibility to injury in the standing position is anticipated; nonetheless, patient position is an important variable to adjust for in statistical models. Patients with VVS are advised to lie down when syncope is anticipated, because this would both help prevent

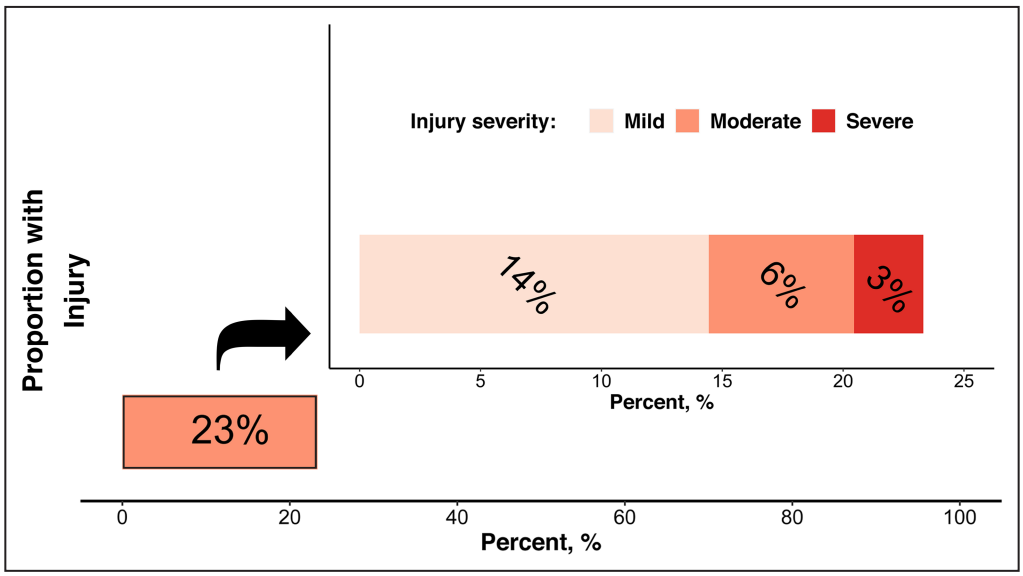


Figure 2. The incidence of injury and its severity during the index vasovagal syncope episode.

Table 2. Characteristics Associated With Moderate-to-Severe Injury in Patients With Vasovagal Syncope

Characteristic	All, n=1115	With moderate-to-severe injury, n=99	Univariate		Multivariable	
			Relative risk (95% CI)	*P* value	Adjusted relative risk (95% CI)	*P* value
Age, y	45.9±17.3	47.2±16.8	1.05 (0.94–1.17)*	0.367	0.98 (0.86–1.10)*	0.711
Sex						
Men	580	43				
Women	535	56	1.41 (0.97–2.06)	0.073	1.53 (1.04–2.25)	0.031
BMI, kg/m^2						
<25	472	32				
≥25	643	67	1.54 (1.03–2.3)	0.035	1.41 (0.94–2.17)	0.104
Recurrent syncope						
First time	305	30				
Recurrent	810	69	0.87 (0.58–1.3)	0.491	0.63 (0.40–1.01)	0.052
Previous injury after syncope						
No	919	69				
Yes	196	30	2.04 (1.37–3.04)	<0.001	2.09 (1.33–3.26)	0.001
Diabetes						
Absent	1049	94				
Present	66	5	0.85 (0.36–2.01)	0.701	0.76 (0.26–1.75)	0.550
Hypertension						
Absent	862	76				
Present	253	23	1.03 (0.66–1.61)	0.893	1.01 (0.59–1.63)	0.984
Anemia						
Absent	918	85				
Present	197	14	0.77 (0.45–1.32)	0.335	0.73 (0.40–1.21)	0.250
Family history of syncope						
Absent	1016	90				
Present	99	9	1.03 (0.53–1.97)	0.938	1.01 (0.49–1.81)	0.973
Syncopal episode time						
Morning	289	36	Reference		Reference	
Noon/afternoon	410	44	0.86 (0.57–1.30)	0.481	0.90 (0.60–1.36)	0.623
Evening/night	416	19	0.37 (0.21–0.63)	<0.001	0.42 (0.24–0.71)	0.001
Syncope occurred at						
Outside home	540	39				
Home	575	60	1.44 (0.98–2.12)	0.059	1.19 (0.81–1.77)	0.391
Specific identifiable triggers						
Absent	655	67				
Present	460	32	0.68 (0.45–1.02)	0.059	0.83 (0.54–1.25)	0.378
Prodromes						
Absent	202	32				
Present	913	67	0.46 (0.31–0.69)	<0.001	0.55 (0.36–0.84)	0.005
Position before syncope						
Sitting or recumbent	440	29				
Standing	675	70	1.57 (1.04–2.38)	0.030	1.30 (0.86–2.02)	0.219

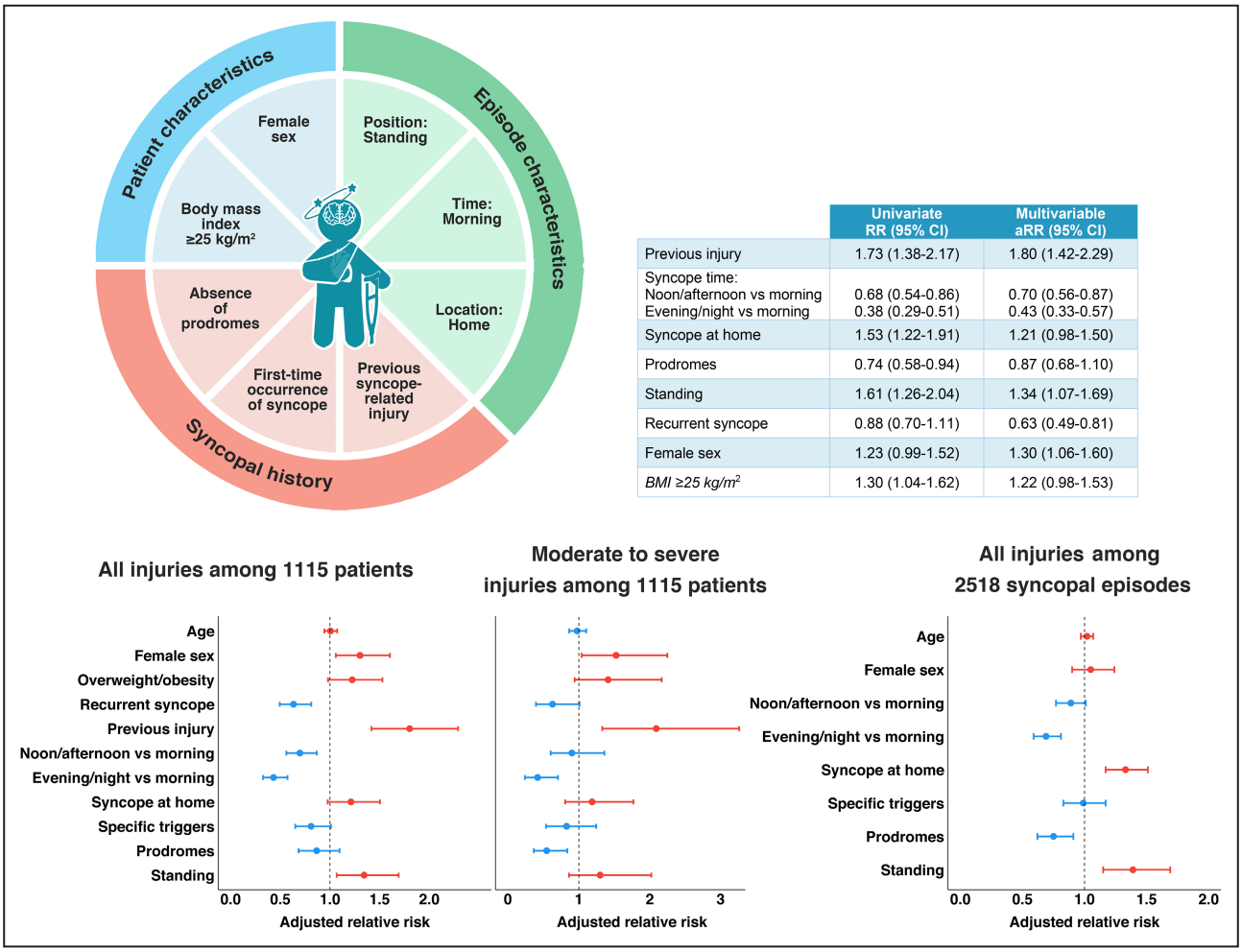
Age is represented as mean±SD. BMI indicates body mass index.
*Relative risks are calculated per 10-year increments for age.

syncope and minimize the risk of injury. The lower rate of traumatic injury in recurrences of VVS may be explained by increased awareness and expectancy of patients and their families, or reflect the efficacy of education and recommendations provided by health care providers. A longitudinal study of 316 patients with VVS referred to the syncope center at Hamburg found that after receiving standard education, the rate

Table 3. Characteristics Associated With Vasovagal Syncope-Related Injury per Syncopal Episodes

Characteristic	All, n=2518	With injury, n=909	Injury risk (95% CI)	Univariate		Multivariable	
				Relative risk (95% CI)	*P* value	Adjusted relative risk (95% CI)	*P* value
Age at the time of syncope, y	44.6±17.2	45.2±17.4	…	1.04 (1.01–1.07)*	0.014	1.02 (0.97–1.07)*	0.513
Sex							
Men	1232	427	0.35 (0.32–0.37)				
Women	1286	482	0.37 (0.35–0.4)	1.08 (0.97–1.2)	0.141	1.05 (0.90–1.24)	0.531
Syncopal episode time							
Morning	675	297	0.44 (0.4–0.48)	Reference		Reference	
Noon/afternoon	940	366	0.39 (0.36–0.42)	0.88 (0.79–0.99)	0.041	0.89 (0.77–1.01)	0.081
Evening/night	903	246	0.27 (0.24–0.30)	0.62 (0.54–0.71)	<0.001	0.69 (0.59–0.81)	<0.001
Syncope occurred at							
Outside home	1237	357	0.29 (0.26–0.31)				
Home	1281	552	0.43 (0.4–0.46)	1.49 (1.34–1.66)	<0.001	1.33 (1.17–1.51)	<0.001
Specific identifiable triggers							
Absent	1406	535	0.38 (0.36–0.41)				
Present	1112	374	0.34 (0.31–0.36)	0.88 (0.79–0.98)	0.022	0.99 (0.83–1.17)	0.889
Prodromes							
Absent	391	183	0.47 (0.42–0.52)				
Present	2127	726	0.34 (0.32–0.36)	0.73 (0.65–0.82)	<0.001	0.75 (0.62–0.91)	0.003
Position before syncope							
Sitting or recumbent	940	253	0.27 (0.24–0.3)				
Standing	1578	656	0.42 (0.39–0.44)	1.54 (1.37–1.74)	<0.001	1.39 (1.15–1.69)	0.001

Age is represented as mean±SD.
*Relative risks are calculated per 10-year increments for age.



	Univariate RR (95% CI)	Multivariable aRR (95% CI)
Previous injury	1.73 (1.38-2.17)	1.80 (1.42-2.29)
Syncope time: Noon/afternoon vs morning Evening/night vs morning	 0.68 (0.54-0.86) 0.38 (0.29-0.51)	 0.70 (0.56-0.87) 0.43 (0.33-0.57)
Syncope at home	1.53 (1.22-1.91)	1.21 (0.98-1.50)
Prodromes	0.74 (0.58-0.94)	0.87 (0.68-1.10)
Standing	1.61 (1.26-2.04)	1.34 (1.07-1.69)
Recurrent syncope	0.88 (0.70-1.11)	0.63 (0.49-0.81)
Female sex	1.23 (0.99-1.52)	1.30 (1.06-1.60)
BMI ≥25 kg/m²	1.30 (1.04-1.62)	1.22 (0.98-1.53)

Figure 3. Patient- and syncope-related associations of injury.
aRR, indicates adjusted relative risk; BMI, body mass index; and RR, relative risk.

of syncope-related injury was reduced from an initial 42% to 25%.[12] Nevertheless, although the history of VVS may be protective, the history of VVS-related injury was associated with a higher risk. This finding was in accordance with the analysis of nationwide registries of Denmark by Numé et al, who found that among patients admitted with all types of syncope, injury risk in the following year was significantly higher if history of prior syncope-related injury was present.[5] This observation suggests that at least part of the risk is attributable to patient-related factors as opposed to episode-related characteristics and signifies the importance of identifying high-injury-risk patients and of care for avoiding recurrences of both syncope and injuries. Because this study lacks prospective data, we were not able to estimate risk of future injury in patients with first-time VVS and compare this risk among those with and without injury in their first VVS episode.

Location of syncope was also an important predictor for injury. The study by Bartoletti et al demonstrated that among patients presenting to the emergency department with syncope, the rate of injury was significantly higher when TLOC occurred at home compared with other settings.[13] A similar finding is observed among patients with seizure, who have a higher risk of suffering a traumatic episode in the home environment.[14] On falls in the elderly, it is suggested that patients with falling at home may be less mobile and frailer[13,15]; however, making the same assumption for patients with VVS is difficult, because these patients are generally young and active. Other factors that differentiate syncope at home versus other settings may be the hazards of falling in bathrooms, or being alone at home at the time of syncope. According to these data, increasing safety at home may be an important recommendation for VVS, especially for patients with high rates of recurrence.

Presence of prodromes is expected to reduce the risk of injury, as was observed in the present study; however, prodromal symptoms have varying severity and duration, and many patients may not be aware of them before syncope.[16] In a pooled analysis of POST

(Prevention of Syncope Trials), POST-2 and POST-4 (fludrocortisone and midodrine in VVS), and POST-3 (pacemaker in syncope with bifascicular block), Jorge et al found that 28% of syncopal episodes in the 2 VVS trials led to injury, but the absence of prodromes was not a predictor of injury.[3] In a study of emergency department visits by Bartoletti et al, however, syncope in the absence of prodromal symptoms was significantly associated with a higher rate of injury, which occurred in 29.5% of syncopal episodes.[13] In light of this discrepancy, it can be suggested that the role of prodromes in preventing injuries depends on other factors such as perception of symptoms of impending syncope, duration of prodromes, and counter-measures taken by the patient.

We found a trend that female patients may be at higher risk of suffering injuries. On the other hand, no association between age and injury can be suggested based on our data. The study by Jorge et al reported that injury risk was not associated with age, but there was a signal for higher risk among women.[3] Among patients with the diagnosis of VVS, Bartoletti et al found a higher risk of injury in orthostatic position, but no differences in syncope-related trauma with regard to age or sex.[13] On the contrary, a recent meta-analysis of injury prevalence among patients with VVS showed that older age was correlated with injury in metaregression and that the rate of trauma in studies with mean age ≤50 years and >50 years was 25.7% and 43.4%, respectively. It should be noted that VVS is more common in younger patients[17]; hence, older individuals may be underrepresented in VVS studies. Furthermore, the risk of injury in patients with advanced age and frailty is not known. Frail patients may suffer from amnesia after a traumatic syncopal episode, and because of the possibility of alternative diagnoses, the assessment of TLOC cause may be inaccurate.[18] Finally, we found a clear signal that overweight and obesity can increase the risk of injury during a syncopal episode. This association is important to consider in future research for the management of VVS.

Clinical Implications of Findings

These results demonstrate that patient-related features, different presentations of VVS, and perisyncopal conditions can determine the risk of injury. Although researchers anticipate accumulation of more data to further characterize predictors of VVS-associated injury, the associations identified herein indicate potential clinical implications and present future research questions.

Patient-related features (history of prior VVS-induced injury, female sex, overweight/obesity) indicate patients with higher risk and could prompt closer follow-ups or a more aggressive approach to prevention of recurrences. VVS episode characteristics, such as absence of prodromes in a prior episode, also help identify high-risk cases and should warn the clinician that a similar recurrence is associated with a higher probability of injury. Furthermore, associations of injury with perisyncopal conditions suggest opportunities to minimize the risk of VVS and injury in a specific setting. For instance, improving the safety at home for patients with frequent episodes, recommending avoidance of suddenly assuming an upright position upon waking up, or drinking more fluids early in the day could be relevant in this regard.

Strengths and Limitations

Although previous data focused on patients enrolled in clinical trials, those with recurrent episodes, or patients presenting to the emergency department, our study considers patients evaluated at a syncope unit irrespective of their recurrence rates and without strict selection. However, patients at a tertiary syncope unit could have inherently different characteristics to the total population with VVS or those presenting to primary care, which limits the generalizability of our results. Diagnosis of VVS was based on expert opinion, which can limit reproducibility of this study; nevertheless, it should be highlighted that the diagnosis of VVS in practice is largely based on clinical evaluation.[8,9] We considered adjustment for different clinical characteristics, a method that was not considered in prior studies with smaller sample sizes and fewer clinical variables, but the probability of residual confounding and the role of other unmeasured factors, such as adherence to therapeutic measures, habitual factors, or education of family members, in modifying the risk of injury cannot be ruled out. Moreover, in the per-syncope analysis, VVS episodes and incidence of injury were considered retrospectively; therefore, caution is advised in interpreting the results of this section. We did not include follow-up data in this analysis; however, because the cohort will continue to enroll and follow up patients, these data will become available and be reported in the future.

CONCLUSIONS

Syncope-related injury is an important outcome in patients with VVS with a considerably high incidence. Prior history of syncope-related trauma, overweight and obesity, and female sex are patient characteristics indicative of injury risk. Moreover, experiencing VVS in the morning, at home, while standing, or in the absence of prodromal symptoms are associated with higher injury rates, and the absence of prodromes is associated with moderate-to-severe injury. Patients and physicians should attempt to minimize the risk of both syncope and injury in these situations and take precautionary measures in high-risk

environments and for high-risk individuals. Future prospective studies can further elaborate the predictors of VVS-associated injury.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Multivariable model for factors most strongly associated with injury

Variables in the model	Adjusted Relative Risk (95% confidence interval)	*P*-value
Presence of previous injury after syncope	1.77 (1.38-2.24)	<0.001
Syncopal episode time		
Morning	Reference	-
Noon/afternoon	0.70 (0.56-0.87)	0.001
Evening/night	0.43 (0.32-0.57)	<0.001
Syncope location: Home	1.26 (1.02-1.57)	0.033
Absence of prodromes	1.19 (0.93-1.49)	0.066
Standing position before syncope	1.33 (1.06-1.70)	0.015
Fist-time syncope	1.59 (1.23-2.00)	<0.001
Female sex	1.27 (1.04-1.56)	0.020
Body Mass Index ≥25 kg/m^2	1.26 (1.02-1.55)	0.036

Area under curve of the model: 0.70 (95% CI: 0.66-0.73)

Table S2. Associations with moderate to severe, and severe injury among patients who experienced syncope-related injuries

	All injuries (n=260)	Moderate to severe injury (n=99)		Severe injury (n=32)	
			Relative risk (95% CI)		Relative risk (95% CI)
Age, years*	46.8 ± 17.4	47.2 ± 16.8	1.01 (0.93-1.11)	45.3 ± 18.1	0.96 (0.79-1.15)
Sex					
Male	122	43 (35.2%)		11 (9%)	
Female	138	56 (40.6%)	1.15 (0.84-1.58)	21 (15.2%)	1.69 (0.85-3.36)
BMI, kg/m^2					
<25	94	32 (34%)		11 (11.7%)	
≥25	166	67 (40.4%)	1.19 (0.85-1.66)	21 (12.7%)	1.08 (0.55-2.14)
Recurrent syncope					
First time	78	30 (38.5%)		11 (14.1%)	
Recurrent	182	69 (37.9%)	0.99 (0.70-1.38)	21 (11.5%)	0.82 (0.41-1.61)
Previous injury after syncope					
No	190	69 (36.3%)		22 (11.6%)	
Yes	70	30 (42.9%)	1.18 (0.85-1.64)	10 (14.3%)	1.23 (0.62-2.47)
Diabetes mellitus					
Absent	243	94 (38.7%)		31 (12.8%)	
Present	17	5 (29.4%)	0.76 (0.36-1.61)	1 (5.9%)	0.46 (0.07-3.18)
Hypertension					
Absent	197	76 (38.6%)		26 (13.2%)	
Present	63	23 (36.5%)	0.95 (0.65-1.37)	6 (9.5%)	0.72 (0.31-1.67)
Anemia					
Absent	215	85 (39.5%)		24 (11.2%)	
Present	45	14 (31.1%)	0.79 (0.49-1.25)	8 (17.8%)	1.59 (0.77-3.31)
Family history of syncope					
Absent	230	90 (39.1%)		25 (10.9%)	
Present	30	9 (30%)	0.77 (0.43-1.36)	7 (23.3%)	2.15 (0.99-4.53)
Syncopal episode time					
Morning	103	36 (35%)		11 (10.7%)	
Noon/afternoon	100	44 (44%)	1.26 (0.89-1.78)	15 (15%)	1.40 (0.68-2.91)
Evening/night	57	19 (33.3%)	0.95 (0.61-1.50)	6 (10.5%)	0.99 (0.38-2.52)
Syncope occurred at					
Outside home	99	39 (39.4%)		16 (16.2%)	
Home	161	60 (37.3%)	0.95 (0.69-1.30)	16 (9.9%)	0.61 (0.32-1.17)
Specific identifiable triggers					
Absent	171	67 (39.2%)		23 (13.5%)	
Present	89	32 (36%)	0.92 (0.66-1.28)	9 (10.1%)	0.75 (0.36-1.56)
Prodromes					
Absent	60	32 (53.3%)		7 (11.7%)	
Present	200	67 (33.5%)	**0.63 (0.46-0.85)**	25 (12.5%)	1.07 (0.49-2.35)
Position before syncope					
Sitting or recumbent	75	29 (38.7%)		10 (13.3%)	
Standing	185	70 (37.8%)	0.98 (0.70-1.37)	22 (11.9%)	0.89 (0.44-1.79)

Age is represented as mean ± standard deviation.

* Relative risks are calculated per 10 years increments for age.