

# Age is a predictor for the recurrence of syncope in vasovagal syncope patients with a positive head-up tilt test

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## Research article

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# Abstract

**BACKGROUND** Valid predictors of the recurrence of syncope in vasovagal syncope (VVS) patients with a positive head-up tilt test (HUTT) are currently lacking. The goal of this study was to identify the predictive performance of age for the recurrence of syncope in VVS patients with a positive HUTT.

**METHODS** In total, 175 VVS patients with a positive HUTT were followed for 6 to 32 months, and  $\geq 1$  syncope episodes during follow-up was considered the recurrence of syncope. The study population was divided into 2 groups, namely, a recurrence of syncope group (44 patients) and a no recurrence of syncope group (131 patients). The baseline clinical data, hemodynamic parameters and classification of the vasovagal syncope on the HUTT were analyzed. Binary logistics regression was used to analyze the effect size and confidence interval of age. A receiver operating characteristic (ROC) analysis was used to assess the predictive performance and investigate the predictive value of age by the area under the curve (AUC).

**RESULTS** The age of recurrence of syncope group 60.0 (47.8, 66.0) years was older than that of no recurrence of syncope group 53.0 (43.0, 62.0) years, and there was a significant difference between the two groups ( $P < 0.05$ ). The trend of syncope recurrence changed with age and the binary logistics regression model adjusted by sex showed that the elder was an increased risk of syncope recurrence in VVS with positive HUTT [OR value: 1.034, 95% confidence interval (CI) 1.008 to 1.061  $p < 0.05$ ]. Age was a valid predictor for the recurrence of syncope in VVS patients with a positive HUTT (AUC: 0.688; 95% CI 0.598 to 0.777  $p < 0.05$ ). The cut-off value was 53.5 years, and the sensitivity and specificity were 72.7% and 52.7%, respectively.

**CONCLUSIONS** Age was a valid predictor for recurrence of syncope in VVS patients with positive HUTT. The rate of recurrence of syncope increased with increasing age, especially in old female.

## Background

Vasovagal syncope (VVS) is challenging to treat as a heterogeneous disorder. The quality of life and mental health of patients could be seriously affected by recurrent VVS [1,2]. Most clinical studies on the treatment of the recurrence of syncope in VVS patients, such as with drugs, were mainly based on head-up tilt test (HUTT) results and the Vasovagal Syncope classification, and then the results of studies were inconsistent [3,4,5,6,7]. Syncope which is severe and refractory to conservative treatment is usually dealt with medical or device therapy. Thus, the valid prediction of recurrent syncope is urgently needed to guide the choice of treatment options. Factors which can best predict the recurrence of syncope after a positive HUTT are little known, despite numerous randomized trials. Older adults usually affect atypical vasovagal syncope, and many of them have little or no prodrome [8]. Sheldon R et al. found that the most powerful predictor of a recurrence of syncope was the logarithm of the number of preceding syncopal spells [9]. We investigated that whether age is an important factor affecting syncope recurrence in VVS patients.

# Methods

## Subjects

In total, 479 inpatient and outpatients with suspected clinically neuro-mediated syncope (NMS) underwent a HUTT in Ningbo Hospital, Zhejiang University from April 2016 to June 2018; 214 patients with a positive HUTT were diagnosed with VVS, which performed in accordance with the Opinion Standard Operating Procedure for Head-up Tilt Test recommended by Chinese experts[9]. All VVS patients underwent a complete physical examination, chest X-ray, biochemical serum tests, echocardiography, and electroencephalography to exclude severe diseases related to the central nervous, cardiovascular, and metabolic systems. Then, they were followed for between 6 and 32 months. This study was approved by the ethics committee of ningbo first hospital and carried out in accordance with the declaration of helsinki. The data for 175 patients with a median age of 55.0 years(44.0 to 63.0 years, range from 15 to 82 years), were finally enrolled in the analysis; data from patients who were lost to follow-up or received medication or pacing were excluded from the analysis.

## HUTT [10]

### preparation

HUTT was strictly performed in accordance with the protocol of the European Society of Cardiology. Cardiovascular active drug treatment should be stopped using for at least 5 half-life period. Drugs and foods were avoided before the test, if not, which could affect normal autonomic nervous system function. HUTT were performed in a quiet, softly lit, temperature-controlled(20 ~ 25°C) room equipped with medical resuscitation facilities, such as defibrillation, apparatus atropine and other [resuscitative](#) drug. Ringer's solution was used in patients who fasted for at least 4h by intravenous drip before HUTT. Clinical basic data of cerebrovascular diseases (including cerebral ischemia, cerebral infarction, epilepsy and so on), hypertension, cardiovascular disease, diabetes (including type 1 or type 2), natural course of disease and number of spells in lifetime were asked for offering.

### baseline HUTT

Patients were secured to the electric st-721 head-up tilt test table with manual control board (Beijing kangjing taike medical device factory) and GE medical CASE series 12-lead synchronous ECG monitor and suntech blood pressure monitor were used for monitoring blood pressure, heart rate and rhythm. Barring a positive response or loss of consciousness, patients were tilted upright at 70° for 20min after lying supine for at least 10 minute with record supine systolic blood pressure, supine diastolic blood pressure, and heart rate. Symptoms, blood pressure, heart rate and rhythm were recorded every 5 minute and additionally recorded every 1 minute within the begging 3 minutes to rule out orthostatic hypotension during the test. Patients were returned to a supine position as soon as the positive response occurred. The test will be terminated if HUTT is positive in basic stage and will go on with SNHUTT.

## sublingual nitroglycerin HUTT

The test process of SNHUTT was the same as that in the basic stage after the sublingual nitroglycerin administration which the baseline HUTT-negative patients received. (3/4 tablet, 0.5mg/ tablet of shandong xinyi pharmaceutical co.LTD.).

## Diagnostic criteria

Syncope or pre-syncope prodrome accompanied with any of decreases in blood pressure or changes of heart rate with an electrocardiogram showing any of sinus arrest and premature junctional contractions and atrioventricular block and cardiac arrest  $\geq 3$  seconds was a positive HUTT response characteristic.

## Positive response type for VVS(9)

### 1. Type 1 (mixed type)

Type 1 is characterized as heart rate fall but not less than 40 beats per minute(bpm) for < 10 seconds at the time of syncope with or without asystole < 3 seconds. Blood pressure decreases prior to the heart rate falls

### 2. Type 2 (cardioinhibitory type) which is classified to 2 subtype.

#### Type 2A (without asystole)

Type 2A is characterized as a ventricular rate below 40 bpm for longer than 10 seconds and asystole < 3 seconds. the blood pressure decrease occurs later than the heart rate fall.

#### Type 2B (with asystole)

Type 2B is characterized as that the asystole > 3 seconds occurs. The heart rate fall coincides with or precedes the blood pressure decrease.

### 3. Type 3 (vasoinhibitory type)

Type 3 is characterized as that SBP or mean pressure decrease  $\geq 20 \sim 30$  mmHg or systolic BP (SBP) is  $\leq 60 \sim 80$  mmHg (1 mmHg = 0.133 kPa). The heart rate does not fall more than 10% from its peak value at the time of syncope.

## Counseling and advice

An overview of the causes of vasovagal syncope and its overall benign outcome were informed to all patients who received advice about increasing dietary salt and fluid intake unless contraindicated. Patients were also coached on how to avoid situations that might provoke syncope such as fatigue, late night, emotional status and so on and requested for sitting down or lying to a supine position if unavoidable.

## Follow-up protocols

The duration of follow-up ranged from 6 to 32 months after HUTT via telephone follow-up. We one by one telephoned all patients. The patients or their parents were required to confirm recurrent syncope, which was defined as  $\geq 1$  syncope or typical pre-syncope prodrome that occurred during the follow-up. Patients who underwent pacing or drug therapy, such as with metoprolol during follow-up were excluded.

## Definitions

Syncope is a transient loss of consciousness due to a transient global hypoperfusion characterized by rapid onset, short duration, and spontaneous complete recovery. Pre-syncope prodrome includes dizziness, headache, chest tightness, shortness of breath, palpitations, sweating, pallor and nausea, blurred vision, nausea, abdominal discomfort and amaurosis. Recurrence of syncope is defined as the recurrence of  $\geq 1$  syncope or typical pre-syncope prodrome during follow-up.

## Statistical analysis

All reported levels of significance are 2 sided. A P value  $\leq 0.05$  was considered statistically significant. Statistical analysis was carried out with SPSS 23.0 software. Continuous variables with normal distributions are expressed as the mean  $\pm$  standard deviation (SD), and comparisons of normally distributed parameters between two groups were performed with a t-test for independent samples. The nonnormally distributed parameters were reported as the median and interquartile range (25% to 75%) and compared by the Mann-Whitney U test. Categorical variables are reported as frequencies and percentages. The data were compared by the McNemar test, and the exact probability method was used when the theoretical frequency was less than 20%. Binary logistics regression was used to analyze effect size and confidence interval of the individual or multiple factors with statistical significance for recurrence syncope according to the independent sample t test or the McNemar test.

The predictive performance of age was evaluated by prediction probability. The ROC curve was utilized to evaluate the predictive value of the predictors and the AUC represented the predictive value. The 95% CI of AUC did not contain 0.5 or a P value  $< 0.05$  confirmed that the factor was a reliable predictor of recurrent syncope in VVS patients with a positive HUTT. The optimal cutoff value was determined as the maximum of the Youden index, which was defined as the sensitivity plus specificity minus 1, where sensitivity and specificity were calculated as proportions.

# Results

## Patient population

In total, 175 VVS patients were included in the analysis after excluding those lost to follow-up and those receiving drug therapy or pacing, and 5 of them were positive on the BHUTT. Forty four (25.1%) VVS patients had  $\geq 1$  recurrence of syncope during follow-up.

## The baseline characteristics

The baseline characteristics of the two groups are shown in Table 1. The age of the recurrence of syncope group was older than that of the no recurrence of syncope group ( $P < 0.05$ ). Other characteristics were not significantly different between groups ( $P > 0.05$ ).

The HUTT characteristics

The HUTT characteristics of the two groups are shown in Table 2. None of the HUTT characteristics were significantly different between groups ( $P > 0.05$ ).

The distribution of patients by months of follow-up

The distribution of patients by months of follow-up is shown in Figure 1; The distribution was inconsistent between the two groups. The average rank of the data shown in table 2 was not significantly different between the groups ( $P > 0.05$ )

The trend of syncope recurrence changed with age

The study population were classified based on age into 8 groups (<20, 20 - 30, 31 - 40, 41 - 50, 51 - 60, 61 - 70, 71 - 80, and >80 years old), and the graph showed that the rate of syncope recurrence increased with age (Figure 2).

Predictive performance of age

Age, as well as sex, BMI, supine diastolic BP(all  $p < 0.15$  in univariate analysis) were included in the binary logistic regression analysis. Only age with statistical significance in univariate analysis (OR value 1.034,  $p = 0.011$ ) and sex (OR value 2.302,  $p = 0.032$ ) were independently associated with syncope recurrence in VVS with positive HUTT in the multivariable model (table 3).

The predictive ability of age according to the ROC curve

The ROC curve of age for the prediction recurrent syncope in VVS patients with a positive HUTT had an AUC of 0.688 (vs. the null hypothesis AUC of 0.5, 95%CI 0.598 to 0.777,  $p < 0.05$ ). A cutoff value of 53.5 years for age yielded high sensitivity (72.7%) and specificity (52.7%) (Fig. 3).

## Discussion

The main finding of this study is that age is a valid predictor of the recurrence of syncope in VVS patients with a positive HUTT in the ensuing follow-up from 6 to 32 months. The cutoff value for age is 53.5 years. Age as a predictor of recurrent syncope fulfills all 3 criteria for the highest level of statistical significance according to single factor analysis, binary logistic regression, and receiver operating characteristic (ROC) curve analysis. In contrast, other factors, such as VASIS classification and the number of syncope episodes, were not statistically significant. Vasovagal syncope (VVS) is often diagnosed by a HUTT and is known to have a benign prognosis; however, recurrent VVS can seriously affect the quality of life and mental health of patients, particularly older adults. Valid predictors for

recurrence of syncope in VVS, especially in VVS patients with a positive HUTT, are very important for the design of efficient, economical, individualized treatment. Sumner GL et al. proposed that the number of syncope episodes in the year preceding presentation was the most powerful predictor of the time to the recurrence of syncope in a referral-based vasovagal syncope population[12]. There was a similar phenomenon in our study in that the rate of the number of  $\geq 3$  lifetime syncopal spells in the recurrence of syncope group tended to be higher than that in the no recurrence of syncope group (50.0% vs.39.7%, respectively), although the difference was not significant. Another important finding was that age was significantly associated with the recurrence of syncope, and the results indicated that age is a valid predictor of the recurrence of syncope in VVS patients with a positive HUTT. The results may be attributed to the following: first, a fall in cardiac output in adults is the dominant hypotensive mechanism because the systemic vascular resistance always remains above the baseline levels[13]. Second, the rate of comorbidities in the recurrence of the syncope group tended to be higher than in the no recurrence of the syncope group ( 63.6% vs. 32.1%, respectively), although the difference was not significant. Third, Yamaguchi Y et al. proposed that among the patients with a positive HUTT, the recurrence rate of syncope after the HUTT was higher in those with LV dysfunction than in those with normal LV function[14], then the relatively older patients often have LV dysfunction because of cardiovascular comorbidities. Fourth, it is well-known that norepinephrine is the junctional transmitter between sympathetic ganglion cells and effectors. Benditt DG et al. discovered greater a Epi/NE ratio in younger patients with syncope than in older patients during tilt-induced vasovagal syncope[15]. Finally, retrogression results in autonomic nerve function damage, and the autonomic nervous system imbalance may be one of the underlying mechanisms[16]. Previous studies showed mixed results that the effects of drugs or pacing prevented vasovagal syncope [3,4,5,6,7]. A blinded, placebo controlled, multicenter, randomized study showed that the age of the patient and the need for isoproterenol to produce a positive tilt test did not predict subsequent significant benefit from metoprolol[5]. This was inconsistent with our findings. That the previous study enrolled younger subjects than those in our study may be the reason for this inconsistency [ mean age,  $42 \pm 18$  years vs.  $53.0(43.0, 62.0)$  years, respectively]. Moreover, the subjects in our study had received nonpharmacological measures other than pacing, such as physiotherapeutic measures and psychological approaches. Our research further confirmed that  $\beta$ -adrenergic blockade may be effective in the prevention of relatively older VVS patients with positive HUTT and that pacemaker could reduce recurrent syncope in patients with recurrent vasovagal syncope in whom clinically relevant asystole had been documented by implantable loop recorder[7]. We believe that it is of great importance for clinical treatment and prognosis to detect valid predictors of recurrent syncope in vasovagal syncope(VVS) patients with a positive HUTT receiving nonpharmacological measures other than pacing based on our research.

## Limitations

The present study also has limitations. First, our study was an open-label, observational, and single-center retrospective study, and selection bias is inevitable. Second, the lack of data of on LV function resulted in the inability to stratify the population. Third, interval from the HUTT to the first recurrence of syncope was observed during follow-up, and the duration of follow-up varied. In addition, there are known

limitations to the AUC statistical method. Randomized controlled studies are essential to assess the predictive value of age.

## Conclusions

Age is a valid predictor for the recurrence of syncope in VVS patients with positive HUTT. The rate of recurrence of syncope increased with increasing age, especially in old female. VVS patients who were  $\geq 53.5$ -years-old with a positive HUTT had a greater possibility of the recurrence of syncope despite receiving nonpharmacological measures other than pacing.

## Abbreviations

VVS vasovagal syncope

HUTT head-up tilt test

ROC receiver operating characteristic

AUC area under the curve

## Declarations

Ethics approval and consent to participate

The study has been granted ethics approval by the ethics committee of Ningbo first hospital and the protocol complied with the Declaration of Helsinki. All participants were fully informed by written consent and written informed consent was obtained from a parent or guardian for participants under 16 years old.

Consent for publication

not applicable.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request

Competing interests

The authors declare that they have no competing interests.

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## Authors contributions

YG participated in the design of the study, data collection and drafting the manuscript. XC conceived the study, participated in its design. TZ and LW and LC participated in the design of the study and data collection. All authors read and approved the final manuscript.

## Acknowledgements

Not applicable.

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## Tables

Age is a predictor for the recurrence of syncope in vasovagal syncope patients with a positive head-up tilt test

Table 1 Baseline Characteristics of the Study Population and follow-up duration

Cases(n=175)	Group A (n=44)	Group B (n=131)	t/ X <sup>2</sup> /Z value	P value
Males / females (n)	13 /31	58 /73	2.964	0.085
Age (yrs)	60.0(47.8,66.0)	53.0(43.0,62.0)	-2.346	0.019
BMI (kg/m <sup>2</sup> )	23.3±3.1	22.4±2.9	1.622	0.107
Patients with comorbidities (n)	28(63.6%)	42(32.1%)	0.275	0.600
Hypertension (n)	11(25.0%)	36(27.5%)	0.103	0.748
Cardiovascular disease (n)	3(6.8%)	7(5.3%)	0.000	1.000
Diabetes (n)	3(6.8%)	4(3.1%)	0.433	0.511
Cerebrovascular disease (n)	1(2.3%)	3(1.5%)	0.000	1.000
Duration of symptoms (less than 2 years)	25(56.8%)	84(64.1%)	0.748	0.387
Number of spells in lifetime (more than 3 times)	22(50.0%)	52(39.7%)	1.433	0.231
Follow-up duration (months)	18.0(14.0,25.0)	16.0(11.0,23.0)	-1.482	0.138

Table2 Baseline positive HUTT Characteristics of the Study Population

Cases(n=175)	Group A (n=44)	Group B (n=131)	t/ X <sup>2</sup> value	P value
Positive BHUTT/ Positive SNHUTT	5/39	6/125	1.550	0.213
HR (bpm)	71.1±15.2	70.47±12.1	0.263	0.793
Supine systolic BP (mmHg)	126.3±19.1	124.7±18.8	0.482	0.630
Supine diastolic BP (mmHg)	78.3±9.9	75.5±11.2	1.469	0.144
Supine heart rate (bpm)	71.1±15.2	70.5±12.1	0.263	0.793
Induced Syncope (n)	19	58	0.016	0.899
Arrhythmic events (n)	4	18	0.648	0.421
Type 1 (mixed type) (n)	19	69	1.187	0.276
Type 2(Cardioinhibitory type) (n)	3	10	0.000	1.000
type 2A (n)	1	5	0.000	0.993
Type 2B (n)	2	5	0.000	1.000
Type 3 (Vasodepressor type) (n)	22	52	1.433	0.231

Table3 Determinants of syncope recurrence in the Study Population

Factor	B value	S.E value	Wald value	P value	Exp(B)	95%CI of Exp(B)
sex	0.834	0.389	4.598	0.032	2.302	1.074 - 4.932
Age	0.034	0.013	6.427	0.011	1.034	1.008 - 1.061

CI confidence interval

## Figures

Age is a predictor for the recurrence of syncope in vasovagal syncope patients with a positive head-up tilt test

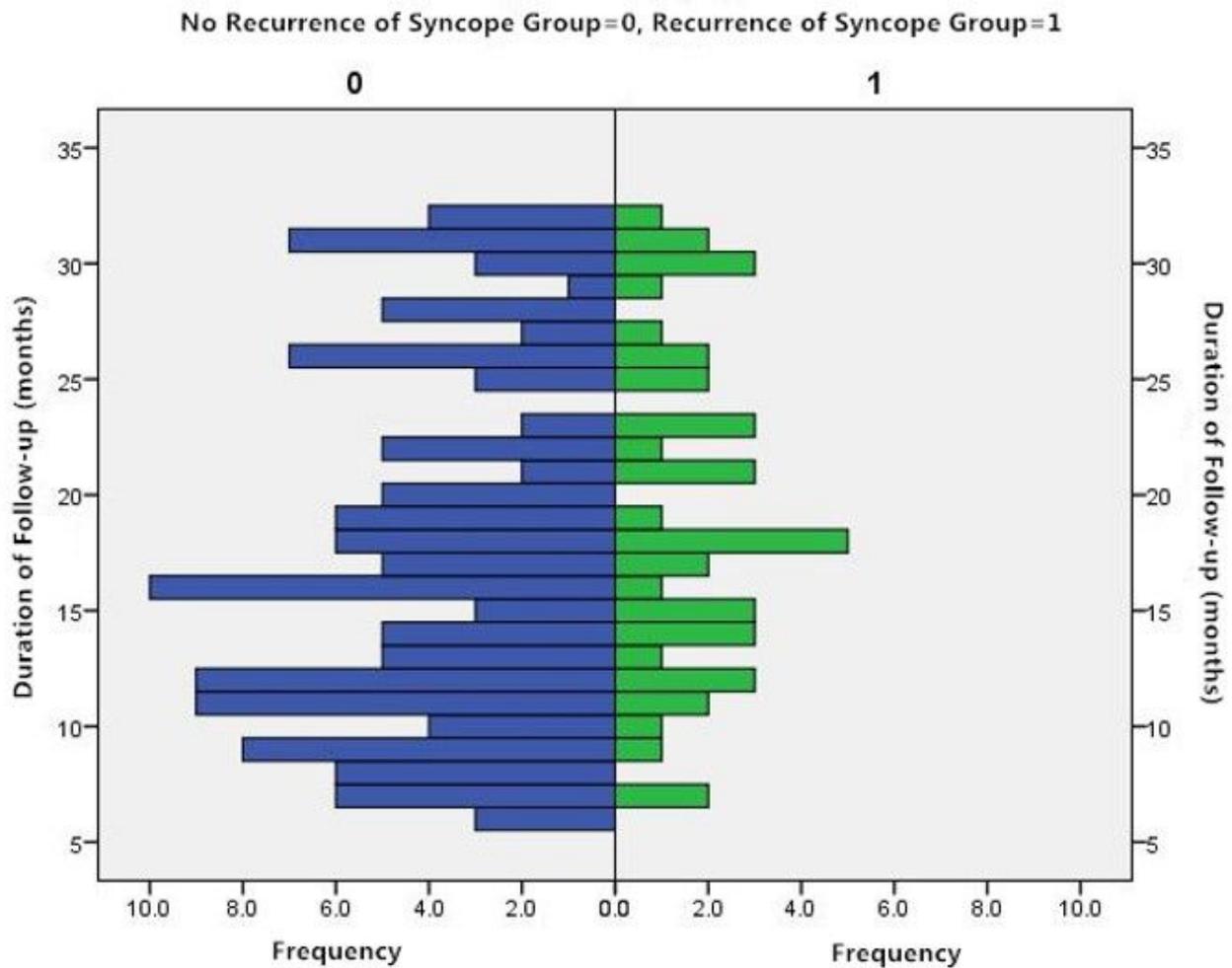


fig 1.

Figure 1

the distribution of patients by months of follow-up

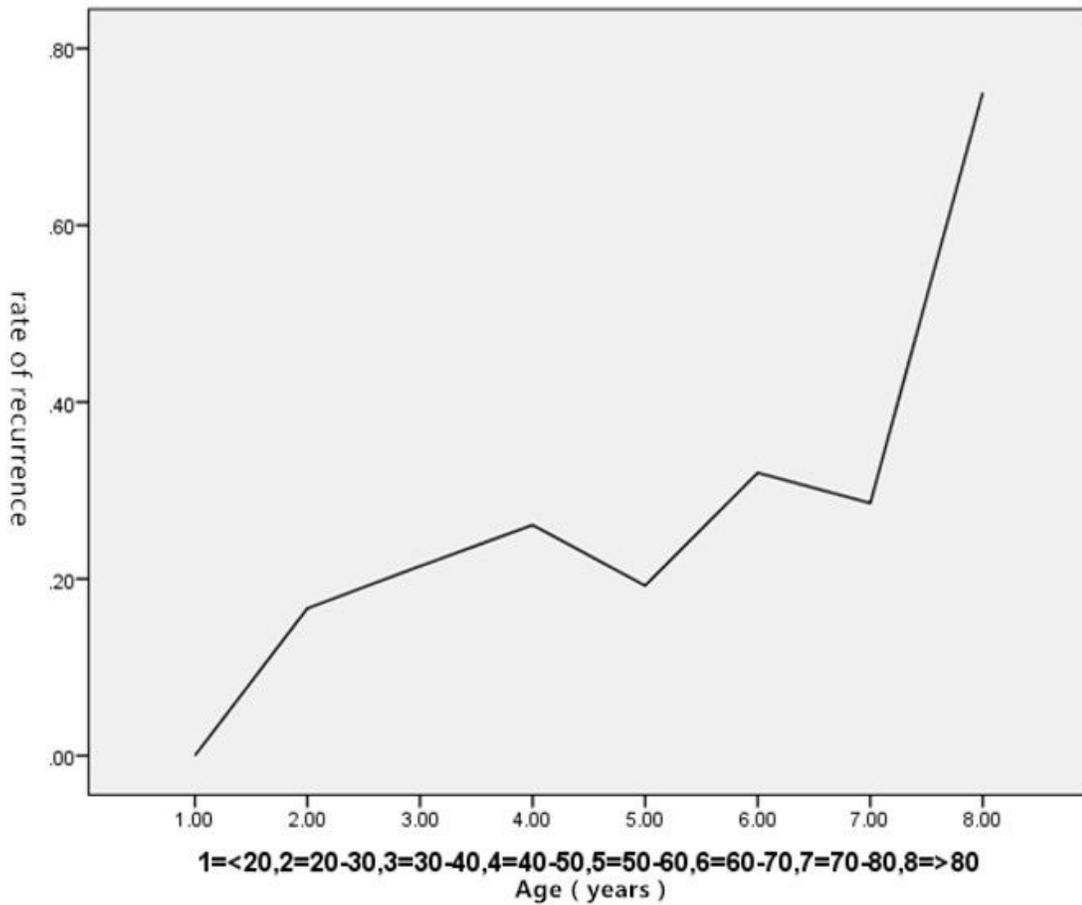
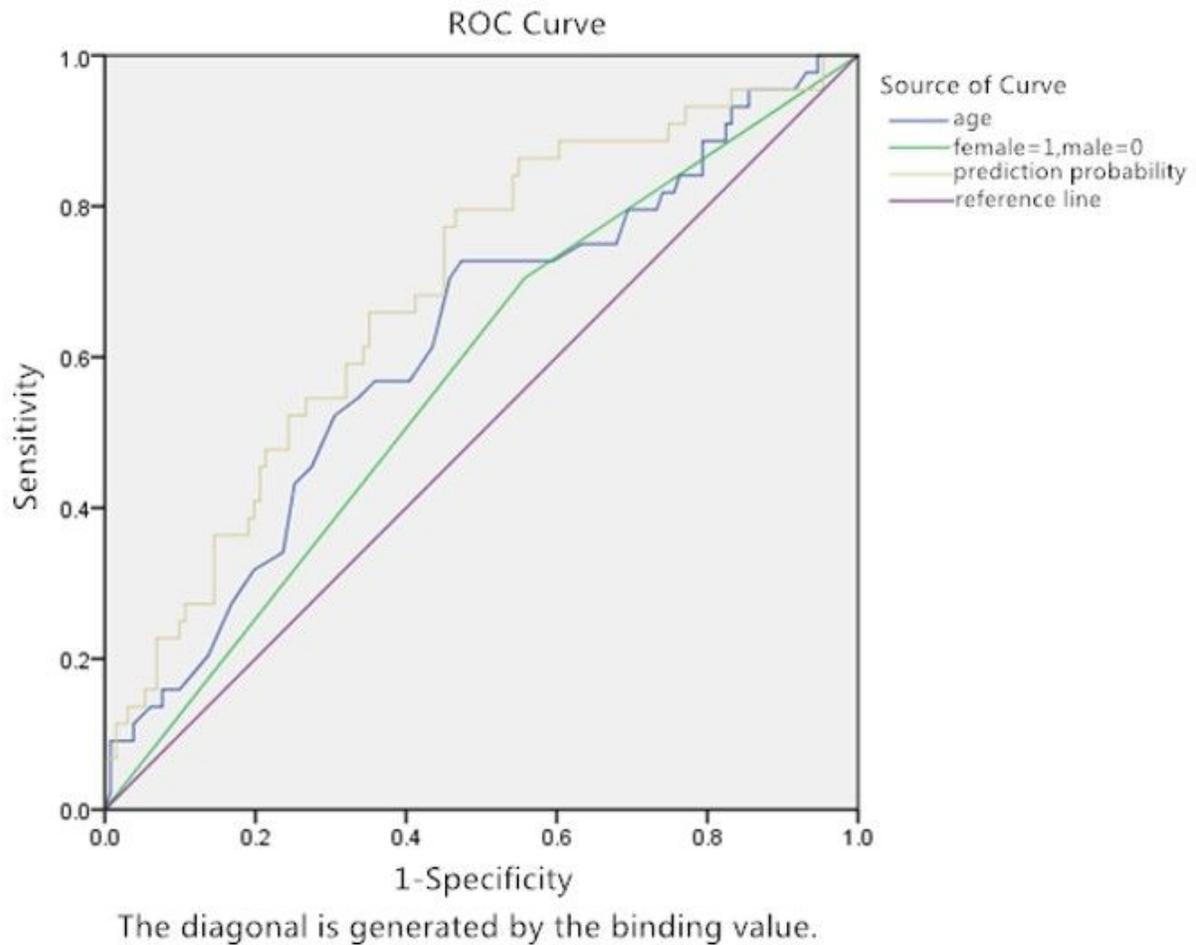


fig 2.

## Figure 2

Age-Trend of syncope recurrence based on the percentage within each age group. The rate of syncope recurrence increased with age showed in figure 2.



**Figure 3**

ROC curve of the predictive value of age for recurrent syncope by prediction probability. The y-axis represents the sensitivity to predict recurrence syncope. The x-axis represents the false positive rate (1-specificity) of prediction. The green line in the graph is the reference line, which indicates the sensitivity being equal to the false positive rate. The blue curve is farther from the green line and nearer to the upper left corner of the graph. The area under the curve is 0.688 (95% CI 0.598 to 0.777,  $P < 0.05$ )