Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

The Diagnostic and Etiological Value of Serum CPT in Differentiating Syncope from Presyncope: A Diagnostic Accuracy Study

Ayça Çalbay

ayca.calbay@atauni.edu.tr

Atatürk University

Mevlana Gül

Atatürk University

Çalbay Murat Maksut

Ministry of Health

Akgöl Gür Sultan Tuna

Atatürk University

Nurinnisa Öztürk

Atatürk University

Murat Daşhan

Atatürk University

Research Article

Keywords: Syncope, presyncope, CPT

Posted Date: June 5th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9741579/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Background

Syncope and presyncope are frequent causes of emergency department (ED) admissions and may reflect a broad spectrum of underlying conditions ranging from benign to life-threatening etiologies. Differentiating syncope from presyncope in the ED remains challenging. Copeptin (CPT), a stress-related biomarker, may aid in this distinction..

Methods

This prospective diagnostic accuracy study included 92 adult patients presenting with syncope or presyncope. Study was conducted in the emergency department of a tertiary university hospital. Demographic data, clinical findings, electrocardiographic results, and routine laboratory parameters were recorded. Serum CPT levels were measured at admission. Diagnostic performance was evaluated using Receiver Operating Characteristic (ROC) curve analysis.

Results

A total of 92 patients were included. CPT levels were significantly higher in syncope patients compared to presyncope (585.4 ± 128.5 vs 406.3 ± 98.0 pg/mL, p = 0.001). The Area Under the Curve (AUC) for CPT was 0.861 (95% CI: 0.79–0.94). At a cut-off of 472.39 pg/mL, sensitivity was 82% and specificity was 75%.

Conclusion

Serum CPT demonstrates good discriminative ability and may serve as a supportive biomarker in differentiating syncope from presyncope in the ED. Further multicenter validation studies are required.

1. Introduction

Syncope is a clinical condition characterized by transient loss of consciousness resulting from a temporary period of inadequate cerebral perfusion/blood flow [1]. It occurs due to a sudden drop in systemic blood pressure to a level that cerebral autoregulation cannot compensate for, thereby falling below the capacity required to maintain adequate cerebrovascular flow. The most prevalent etiologies of syncope encompass reflex (neurally mediated) events, orthostatic hypotension, and cardiac complications. Typically, syncope caused by hypotensive factors is relatively brief, lasting approximately 8 to 10 seconds. The etiology of this condition is distinct from other causes of loss of consciousness, such as seizures or hypoglycemia, by virtue of both its underlying mechanism and its recovery pattern [2].

Recovery from true syncope is generally complete and rapid, and episodes rarely exceed 1 or 2 minutes in duration. If the actual or apparent loss of consciousness persists for a longer period, this suggests that the event may not be syncope or may not be solely attributable to syncope (e.g., syncope resulting in trauma, thereby prolonging the event).

When syncope is directly observed by a physician or reproduced under laboratory conditions, determining the etiological diagnosis may not pose a significant challenge. However, when a patient presents to the emergency department due to syncope, there may be some doubts concerning both the diagnosis and etiology. Diagnostic evaluations can be time-consuming, costly, and frequently ineffective, as the underlying cause of syncope remains unidentified in 2–36% of cases [3, 4].

Presyncope (or near-syncope) is a clinical symptom suggestive of impending syncope, often accompanied by a series of prodromal symptoms similar to those observed in syncope, including dizziness, nausea, sweating, weakness, and visual disturbances. It reflects conditions that may lead to syncope in the same individual at different times. The most crucial distinguishing feature of presyncope is the absence of loss of consciousness. However, it remains unclear whether the underlying pathophysiological mechanisms in presyncope are identical to those in syncope [5]. Presyncope (i.e., near syncope or near loss of consciousness) and true syncope should be considered as different degrees of the same symptom. They can be evaluated as different spectrums of the underlying pathology. Although presyncope is less dramatic, emergency room physicians assess the patient using a similar approach [6–8]. It is important to note that both syncope and presyncope can signal serious underlying conditions, especially in the context of acute illnesses such as pulmonary embolism, where both are associated with an increased risk of adverse outcomes and may require similar levels of clinical caution. Although less dramatic, presyncope has the capacity to predict significant short-term risks, including arrhythmias and other serious outcomes, particularly in older adults or those with comorbidities [9, 10].

International syncope researchers are working on defining syncope, its consequences and management priorities [11, 12]. The current state of research does not yet allow for a definitive conclusion regarding the consistency or difference in biomarker levels between presyncope and syncope [13]. Clearly identifying the right patients has led, and will continue to lead, to progress and improvements in the management of these patients in the emergency department (ED) [14].

CPT, a stable peptide derived from the precursor of vasopressin, has emerged as a promising biomarker in a range of neurological disorders [15, 16] with particular relevance to traumatic brain injury and stroke [17–19]. Its measurement offers insights into disease severity, prognosis, and potential diagnostic value, especially in cases where vasopressinergic dysfunction is implicated. Its potential benefits in other conditions, such as febrile convulsions and eating disorders, are encouraging. However, further research is required to elucidate its role in syncope and presyncope. The measurement of CPT has the potential to enhance clinical decision-making and individualized patient care in this patient group. The potential of CPT as a suitable biomarker for syncope can be attributed to two main factors. Firstly, the global

cerebral hypoperfusion responsible for the loss of consciousness in syncope results from arterial hypotension, which is a stimulus for vasopressin secretion. Secondly, syncope is characterized by a state of stress, and vasopressin functions as a stress hormone. It has been hypothesized that CPT levels are associated with an individual's stress levels and that they are indicative of a poor prognosis in various acute conditions [20].

CPT levels have been observed to increase in response to the stress and hypotension associated with syncope, thus rendering it a potential biomarker for distinguishing syncope from analogous conditions such as presyncope. Nevertheless, the prevailing guidelines do not currently encompass the utilization of CPT as a conventional diagnostic instrument, and its clinical efficacy remains subject to ongoing evaluation [20, 21]. Similarly, a limited number of studies have evaluated CPT measurements in cases of syncope. These studies have yielded preliminary findings suggesting an association between high CPT levels and cardiac syncope and poor prognosis. However, the patient groups were heterogeneous and the sample sizes were small. [21, 22]

The objective of this study;

1. To evaluate the diagnostic and etiological significance of serum CPT levels in patients presenting to the emergency department with complaints of syncope or presyncope.

2. To investigate whether a prognostically significant cut-off value could be determined for serum CPT levels in identifying life-threatening causes of syncope, including those of cardiac origin, central nervous system involvement, gastrointestinal bleeding, or pulmonary embolism.
3. To investigate the potential for integration into clinical triage algorithms by combining pre-hospital CPT measurements with the patient's clinical presentation.
4. To establish a guiding CPT threshold for cases in which patients are unable to describe their syncope or presyncope episodes. This would prevent the oversight of life-threatening conditions.
5. In high-acuity emergency service units that manage critical patients, the objective is to reduce prolonged and unnecessary hospital stays by preventing extensive and redundant diagnostic evaluations in patients unable to describe their syncopal or presyncopal events.

2. Material and methods

2.1 *Study Design*

This study was designed as a prospective diagnostic accuracy study aimed at evaluating the ability of serum CPT levels to discriminate between syncope and presyncope in the emergency department setting. It was conducted between 15.09.2023 and 15.06.2024 at the Emergency Medicine Departments of Atatürk University Research Hospital. The study commenced after receiving approval from the Atatürk University Clinical Research Ethics Committee (date: 07/09/2023, protocol code: B.30.2.ATA.0.01.00/1 and number: B.30.2.ATA.0.01.00/607). Written informed consent was obtained from all volunteers participating in the study. For patients who arrived unconscious, consent was obtained from their legal

guardians. The study was conducted in accordance with the Declaration of Helsinki and good clinical practices. All patients presenting to the emergency department with syncope or presyncope during the study period were included as participants. Although the study was planned prospectively, epidemiological data from patients and data from samples collected from patients were collected and recorded only after obtaining ethical committee approval.

The sample calculation, conducted using G Power 3.1.9.7 (Franz Faul, Germany), used data from Flevari P (2017) and colleagues' study "CPT levels in patients with vasovagal syncope." The effect size was determined to be d = 0.5. The calculation, which was performed with 80% power and a 0.05% margin of error, was planned to include at least 51 patients in each group, resulting in a total of 102 patients [15].

During the study period, 122 patients presented to the Emergency Medicine Department of Atatürk University Research Hospital with complaints of syncope or presyncope. Inclusion criteria were being at least 18 years old, not pregnant, and presenting to the emergency department with a syncope or presyncope. Patients were excluded due to syncope/pre-syncope secondary to Cardiopulmonary arrest, status epilepticus, stroke, sepsis, hypoglycemia (blood glucose < 60 mg/dL), active intoxication or drug overdose, severe anemia (Hb < 8 g/dL) or a known hematological malignancy, end-stage renal or hepatic failure, pregnancy, or inability to obtain vascular access or sufficient sample volume were excluded from the study. A total of 92 patients met the study criteria and were included. Patients were divided into two groups based on clinical findings. Patients experiencing altered consciousness along with loss of postural tone formed the syncope group, while those who did not experience syncope formed the presyncope group (Fig. 1). Patients were consecutively enrolled during the study period.

In our study, patients taking medications and those with comorbidities were excluded because serum CPT levels may be affected.

2.3. Intervention

Upon hospital admission, patients had blood samples drawn for diagnostic tests, including Hb(Hemoglobin), Hct(Hemotocrit), MCV(Mean Corpuscular Volume), ph, Pco2, HCO3, Lactate, Base excess, Troponin I, lactate dehydrogenase activities, as well as calcium, magnesium, and glucose levels. Laboratory analyses were performed on serum separated by centrifugation. Additionally, 2cc of serum was stored at -80°C for batch analysis of CPT. Epidemiological, medical history, electrocardiographic evaluations and underlying causes were recorded. Routine emergency department management was applied for the diagnosis and treatment of patients.

2.4. Biochemical Analysis

Blood samples were collected from the antecubital region of patients presenting with syncope or presyncope. The samples were obtained by experienced personnel using vacutainer systems and collected into green-capped biochemistry tubes with mechanical separators (BD Barricor, Becton Dickinson). The blood samples were allowed to rest at room temperature for 5 minutes. Following clot

formation, the samples were centrifuged, and serum samples were separated. The serum samples were stored at − 80°C until analysis. Prior to analysis, the samples were thawed under appropriate laboratory conditions, and repeated freeze–thaw cycles were avoided to preserve sample integrity. To minimize analytical variability, all biochemical analyses were performed in a single session at the Medical Biochemistry Laboratory of Atatürk University Health Research and Application Center Directorate.

Serum CPT levels were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Cat No: ABT1470 Hu, Atlas Biotechnology Co., Ltd., Ankara, Turkey) in accordance with the manufacturer's standard protocol. Measurements were performed using an ELISA reader (BioTek PowerWave XS, USA). Calibration and internal quality control procedures were conducted according to the kit instructions to ensure assay performance. All samples were analyzed in duplicate, and the mean values were used for statistical analysis to ensure analytical reliability. The intra- and inter-assay coefficients of variation for the kit were reported to be < 10%.

Blood gas parameters, including base deficit, were measured using an ABL800 FLEX device. Hemoglobin (Hb), hematocrit (Htc), and mean corpuscular volume (MCV) levels were measured using a Mindray BC-6800 Plus device. Troponin levels were measured using the Beckman Coulter DXI 800 immunoassay system (Beckman Coulter Inc., Brea, USA) via the chemiluminescence method. Creatinine kinase and lactate dehydrogenase activities, as well as calcium, magnesium, and glucose levels, were analyzed using the Beckman Coulter AU 5800 clinical chemistry analyzer (Beckman Coulter Inc., Brea, USA) via the photometric method.

2.5. Bias

Potential sources of bias should be considered. First, the single-center design may offer selection bias. Second, CPT levels may vary depending on the time interval between symptom onset and blood sampling, introducing timing bias. Finally, measurements were based on a single time point, limiting assessment of biomarker kinetics. However, laboratory personnel were unaware of clinical information. Clinicians made diagnoses without seeing CPT results.

2.6. Statistical Analysis

Statistical analyses were performed using SPSS version 20.0 (SPSS, Chicago, IL, USA). The normality of parameter distributions was assessed using the Kolmogorov-Smirnov test. The independent-samples t-test (Student' t-test) and the Mann-Whitney test were employed for comparisons of parameters exhibiting a normal distribution. Results were presented as mean ± standard deviation and minimum–maximum values. A significance level of $p < 0.05$ was considered statistically significant.

The receiver operating characteristic curve, representing the predictive power of a specific method, was used to calculate the sensitivity, specificity, area under the curve (AUC), and cut-off value of serum CPT. The optimal cut-off value for CPT was determined using the Youden index. Additionally, multivariable logistic regression analysis was performed to assess whether CPT independently predicted syncope

after adjusting for potential confounders including age, sex, and ECG findings. No indeterminate test results were found in any of the samples, and there was no missing data.

3. Results

A total of 92 patients were included in the study. No significant sex differences were observed among the participants (male/female = 44/48). Additionally, no significant difference in age was found between the two groups ($p = 0.78$). Among the laboratory parameters assessed for the differentiation of syncope and presyncope, only serum CPT levels yielded a potential diagnostic biomarker (Table 1) (Fig. 2).

Table 1
Epidemiological and Clinical variables of participants

Age	**Syncope (n = 45)**	**Presyncope (n = 47)**
	45.8 ± 19.3	**44.6 ± 19.1**
Gender n(%)		
Male	23 (25%)	21 (23%)
Female	22 (24%)	26 (28%)
Loss of postural tone count n(%)		
Single	36 (39.1%)	44 (47.8%)
Multiple	9 (9.8%)	3 (3.3%)
Syncope/presyncope duration n(%)		
< 1 minute	13 (14.1%)	19 (20.6%)
1–5 minutes	24 (26.1%)	18 (19.6%)
> 5 minutes	8 (8.7%)	10 (10.9%)
Hospital access time n(%)		
< 1 Hour	35 (38.1%)	27 (29.3%)
1–2 Hour	4 (4.3%)	10 (10.9%)
> 2 Hour	6 (6.5%)	10 (10.9%)
Incontinence (n) (%)		
None	39 (42.4%)	42 (45.7%)
Urinary incontinence	1 (1.1%)	4 (4.3%)
Fecal incontinence	2 (2.2%)	0 (0%)
Mix	2 (2.2%)	1 (1.1%)
Outcome (n) (%)		
Discharged	34 (36.9%)	45(48.9%)
Service	8 (8.7%)	1 (1.1%)
İntensive care unit	3 (3.3)	1 (1.1%)
ECG Rhythm n(%)		
Sinus rhythm	34 (36.9%)	43 (46.7%)
(ECG: Electrocardiogram, AV: atrioventricular)		

Age	Syncope (n = 45)	Presyncope (n = 47)
	45.8 ± 19.3	**44.6 ± 19.1**
Sinus tachycardia	7 (7.6%)	2 (2.2%)
First degree AV block	2 (2.2%)	1 (1.1%)
Left branch block	1 (1.1%)	0 (0%)
Atrial fibrillation	1 (1.1%)	1 (1.1%)
(ECG: Electrocardiogram, AV: atrioventricular)		

Table 1 Epidemiological and Clinical variables of participants

Routine laboratory parameters, and CPT levels of patients are presented in Table 2 as mean ± SD and p values.

Table 2
Comparison of laboratory parameters according to presence of syncope/presyncope

Laboratory parameter	Syncope	Presyncope	p-value
Calcium (mg/dL)	9.08 ± 0.61	9.17 ± 0.62	0.485
Magnesium (mg/dL)	1.89 ± 0.38	1.92 ± 0.33	0.625
Lactate dehydrogenase (U/L)	258.10 ± 115.16	294.38 ± 123.81	0.149
Lactate (mmol/L)	1.81 ± 0.93	1.88 ± 1.18	0.771
pH	7.40 ± 0.04	7.39 ± 0.07	0.627
pCO_2 (mmHg)	39.12 ± 7.33	39.48 ± 6.75	0.807
pO_2 (mmHg)	59.71 ± 12.86	53.81 ± 19.56	0.092
Base deficite	0.07 ± 2.60	0.17 ± 3.67	0.716
Hemoglobin	13.39 ± 2.12	13.45 ± 2.04	0.880
Hematocrit	39.70 ± 7.42	41.07 ± 5.81	0.328
MCV	84.10 ± 6.13	84.00 ± 7.27	0.943
Serum CPT level (pg/mL)	585.41 ± 128.49	406.26 ± 98.01	**0.001**
(Ca: Calcium, Mg: Magnesium, pO_2: partial pressure of oxygen, pCO_2:Partial carbon dioxide, HCO_3:Bicarbonate, LDH:Lactate dehydrogenase, MCV: mean corpuscular volume, SD: standard deviation)			

Table 2. Comparison of laboratory parameters according to presence of syncope/presyncope

At a cut-off value of 472.39 ng/L, serum CPT levels exhibited 82% sensitivity and 75% specificity in differentiating between 45 syncope cases and 47 presyncope cases. The positive predictive value was 59%, while the negative predictive value was 73% (AUC: 0.861, $p < 0.001$, 95% confidence interval (CI): 0.79–0.94, negative likelihood ratio: 0.24, positive likelihood ratio: 3.28) (Fig. 3).

Of the 92 patients, 80 presented to the emergency department with a single episode, whereas 12 had multiple episodes of syncope or presyncope. The duration of consciousness alteration was less than 1 minute in 13/19 syncope/presyncope cases, whereas it exceeded 5 minutes in 8/10 cases. Urinary incontinence was reported in five patients (syncope/presyncope = 1/4), while fecal incontinence was documented in two patients (both syncope cases). Among the participants, 62/92 patients reached the emergency department within 1 hour, while 16/92 had an access time exceeding 2 hours. In patients who presented to the hospital 2 hours after experiencing syncope/presyncope, the mean CPT levels were measured as 596.31 pg/mL in the syncope group and 334.74 pg/mL in the presyncope group.

Upon comparison of the emergency department diagnoses and underlying causes of syncope/presyncope (Table 2) in study population, cardiovascular diseases were identified as the most frequent etiological factor (7/6), followed by pulmonary (4/6) and psychological (5/5) causes. Electrocardiograms (ECGs) obtained upon admission predominantly showed sinus rhythm (34/43), with no significant pathognomonic findings (Table 1).

Table 3 Underlying causes of syncope/presyncope cases in the emergency department

Table 3
Underlying causes of syncope/presyncope cases in the emergency department

Etiology	Syncope (n = 45)	Presyncope (n = 47)	Total (n = 92)
Environmental factors n(%)	4 (4.3%)	4 (4.3%)	8 (8.7%)
Pulmonary cause n(%)	4 (4.3%)	6 (6.5%)	10 (10.9%)
Psychological n(%)	5 (5.4%)	5 (5.4%)	10 (10.9%)
Dehydration n(%)	4 (4.3%)	3 (3.3%)	7 (7.6%)
Allergy n(%)	2 (2.2%)	2 (2.2%)	4 (4.3%)
CVA n(%)	7 (7.6%)	6 (6.5%)	13 (14.1%)
CVE n(%)	4 (4.3%)	4 (4.3%)	8 (8.7%)
Trauma* n(%)	3 (3.3%)	2 (2.2%)	5 (5.4%)
Metabolic disorder n(%)	3 (3.3%)	2 (2.2%)	5 (5.4%)
Sleeplessness n(%)	2 (2.2%)	3 (3.3%)	5 (5.4%)
Infection n(%)	3 (3.3%)	1 (1.1%)	4 (4.3%)
Other n(%)	4 (4.3%)	9 (9.8%)	13 (14.1%)

(AV: atrioventricular, CVA: cerebrovascular accident, CVE: cardiovascular event *The syncope/presyncope in these cases are witnessed situations. The trauma experienced is the trauma observed in the patient during/after the syncope/presyncope. First, the syncope/presyncope is discussed, then the trauma resulting from it.)

It was determined that 34 patients with syncope and 45 patients with presyncope were discharged. Among the final outcomes, three patients with syncope and one patient with presyncope required intensive care unit admission. Four patients had a hospital stay of ≥ 5 days, one of whom was admitted for presyncope. Primary outcome of the study is discriminative ability of serum CPT levels to differentiate syncope from presyncope (AUC of ROC analysis). Secondary outcomes are association with etiological categories and prediction of ICU admission / hospitalization.

4. Discussion

In this study, we investigated the utility of serum CPT levels as a diagnostic and etiological determinants in patients presenting to the hospital with syncope/presyncope. This is the first study in the literature to evaluate the role of CPT in differentiating syncope and presyncope. Our findings showed that serum CPT levels are diagnostic in distinguishing between syncope and presyncope.

In this study, there were no significant differences between the two groups in terms of sex or age. The mean age was 45.8 ± 2.8 years in the syncope group and 44.6 ± 2.7 years in the presyncope group. In comparison with the cohorts examined by Schiavon et al. and Lagi et al., the present cohort is both

younger and has a more controlled comorbidity profile. Schiavon et al. reported a group of older subjects (mean age ~ 65) with frequent cardiovascular and vestibular disorders, while Lagi et al. examined mostly healthy middle-aged adults (mean age ~ 50) compared to healthy controls. Conversely, the present study incorporated all adults aged ≥ 18 years who presented acutely with syncope or presyncope (mean age ~ 45), excluding those with severe anemia, end-stage organ failure, hypoglycemia, pregnancy, or poisoning. This approach provides a more etiologically homogeneous sample, encompassing a broader adult age range, and enhances the generalizability of CPT as a marker for true syncope versus presyncope. [20, 21]. Similar to the research undertaken by Rash et al. [22], our sample comprised a middle-aged population. When analyzing the male-to-female ratio, a relative predominance of females (26/21) was observed among patients with presyncope, whereas no significant sex disparity was noted among syncope cases (22/23), in contrast to the studies by Luca et al. and Lagi et al. [20, 21]. The similar number of female and male cases in both groups prevented potential gender-based differential measurements of CPT levels.

A 2018 study by Robert D. Nass et al. noted that CPT levels declined within 2 hours and returned to baseline 6 hours after a seizure. In our study, CPT levels measured in individuals who experienced syncope/presyncope symptoms more than 2 hours prior were found to be higher than the average levels, particularly in the syncope group. Patients who presented to the hospital within 2 hours of experiencing syncope had an average CPT level of 517.56 ng/L, a value associated with serious clinical outcomes. The short duration between symptom onset and hospital admission may have negatively influenced the correlation between CPT levels and the severity of underlying causes. If CPT levels could be measured before hospital presentation, it might be possible to identify critical underlying diagnoses. Furthermore, pre-hospital CPT measurements could help prevent adverse prognoses in patients.

Furthermore, the prehospital measurement of CPT has the potential to facilitate more expeditious risk classification, thereby mitigating the occurrence of adverse outcomes. In the present series, arrhythmias manifested with a significantly higher frequency in syncope patients (11 cases) compared to presyncope patients (4 cases). This observation indicates a threefold increase in the prevalence of arrhythmias, and these abnormalities were found to be associated with elevated levels of CPT [23, 24]. Despite the existence of prior research that has identified electrocardiographic (ECG) alterations, including ST segment deviations and atrial fibrillation, in patients experiencing syncope, none of these studies have specifically investigated this association [5, 25]. This study is the first to examine the relationship between ECG findings and serum CPT levels in patients with syncope/presyncope.

During the study period, 11 different underlying causes were identified in patients presenting to the emergency department with syncope or presyncope. Laboratory evaluations of the collected blood samples sought to determine a predictive parameter for these underlying causes [26–30]. Apart from serum CPT levels, no other laboratory parameter was found to be a significant diagnostic indicator of syncope or presyncope.

The analysis of emergency department diagnoses revealed that cardiac and pulmonary etiologies were predominant, with psychological factors observed in approximately half of the cases. The mean serum CPT concentrations were 462.82 ng/L in patients with cardiac causes and 534.46 ng/L in those with pulmonary causes. These findings corroborate the observations made by Badertscher et al. of elevated CPT levels in cases of cardiac syncope. [31] Furthermore, the present study validates the efficacy of serum CPT measurement in distinguishing between syncope and presyncope.

Among the hospitalized patients, three with syncope and one with presyncope required intensive care unit admission. The mean CPT levels were 513.84 ng/L for the syncope group and 468.39 ng/L for the presyncope group. In accordance with the cut-off value determined in this study (472.39 ng/L), CPT was found to be effective in distinguishing syncope from presyncope. Furthermore, the results suggest that patients presenting with presyncope may also have serious underlying diagnoses necessitating intensive care, similar to those with syncope.

At a cut-off of 472.39 ng/L, the biomarker demonstrated an 82% sensitivity and 75% specificity for differentiating syncope from presyncope, reflecting substantially higher sensitivity compared to the findings reported by Schiavon et al. The reported figure was 50.0% (95% CI: 30.6–69.4), which is comparable to the 84.6% (95% CI: 65.1–95.6) specificity figure, with a corresponding positive predictive value (PPV) of 77.8% (95% CI: 48.7–94.5) and a negative predictive value (NPV) of 61.1% (95% CI: 46.5–74.3)[20].

Serum CPT levels have been demonstrated to exhibit a high degree of diagnostic accuracy in differentiating syncope from presyncope (AUC ≈ 0.85–0.90). The utilization of an optimal cut-off value, as determined through clinical practice, facilitates the expeditious identification of critical patients, thereby enabling the prioritization of treatment or further investigation.

Limitations of the study

The present study is subject to several limitations. Firstly, the single-center design of the study may restrict the generalizability of the findings to other populations and care settings. Secondly, although the study was powered to detect a moderate effect size, the modest sample size of 92 patients limits the capacity for extensive subgroup analyses and may have been underpowered to detect smaller differences. Thirdly, as a prospective observational investigation, residual confounding—such as variations in prehospital care, hydration status, or vasopressor use—cannot be excluded, and causal inferences are limited. Fourthly, the rigorous exclusion criteria employed in this study, while ensuring cohort homogeneity, may result in a reduction of real-world applicability by omitting patients with common comorbidities such as severe anemia or organ failure. Fifthly, the measurement of CPT was taken at a single time point rather than over a series of time points, thus precluding the analysis of its kinetic profile. Finally, the outcomes were confined to acute disposition (ICU admission and hospital length of stay) without assessment of longer-term endpoints such as 30-day mortality or readmission, which would have reinforced the conclusions on prognosis.

The absence of standardized timing for blood sampling represents methodological constraint. In our study, the interval between syncope/presyncope onset and blood sampling varied among patients. To standardize the time passed after a syncope/presyncope for blood samples collected from patients, the arrival time to the hospital has been selected as the blood collection time. Because serial measurements were not performed, we were unable to assess temporal changes in CPT concentrations. Consequently, intergroup differences may partially reflect variability in sampling time rather than true biological differences, thereby limiting comparability beyond patients.

Conclusion

In this prospective diagnostic accuracy study, involving 92 adults presenting with syncope or presyncope, we demonstrated that serum CPT levels measured upon hospital arrival provided a robust diagnostic distinction between true syncope and presyncope. In contrast to other conventional laboratory parameters, CPT levels demonstrate a correlation with underlying etiologies, particularly cardiac and pulmonary causes and rhythm disorders, thereby underscoring their pathophysiological significance. The balanced cohort, strict exclusion criteria, and single-assay testing methodology employed enhance internal validity. The proposed triage algorithm provides a practical framework for integrating CPT into emergency department workflows to prioritize high-risk patients and reduce unnecessary testing and hospitalizations. Although CPT demonstrated good discriminative ability, it should be interpreted as a supportive biomarker rather than a definitive diagnostic tool. Further multicenter studies with larger populations and external validation are required. The findings of these studies will ultimately contribute to the development of evidence-based guidelines for the management of syncope in the emergency department.

Abbreviations

ED
Emergency Department
CPT
Copeptin
ROC
Receiver Operating Characteristic
AUC
Area Under the Curve

Declarations

Ethics approval and consent to participate

The study commenced after receiving approval from the Atatürk University Clinical Research Ethics Committee (date: 07/09/2023, protocol code: B.30.2.ATA.0.01.00/1 and number:

B.30.2.ATA.0.01.00/607). Written informed consent was obtained from all volunteers participating in the study. For patients who arrived unconscious, consent was obtained from their legal guardians. The study was conducted in accordance with the Declaration of Helsinki and good clinical practices.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing Interests

No, there are no competing interests.

Funding Declaration

Ataturk University Scientific Research Projects Management System project İD: 14684, Project Code: TCD-2024-14684

Author contributions

Çalbay A: Conception, Design, Supervision, Materials, Analysing and/or Interpretation, Literature review, Writer, Critical Review

Çalbay MM: Conception, Materials, Literature review, Critical Review

Akgöl Gür ST: Conception, Supervision, Data collection and/or Processing, Critical Review

Öztürk N: Design, Supervision, Materials , Analysing and/or Interpretation, Critical Review

Gül M: Conception, Design, Data collection and/or Processing, Analysing and/or Interpretation, Critical Review

Daşhan M: Materials , Analysing and/or Interpretation, Literature review

Acknowledgments

Not applicable

References

1. Benditt D, Fedorowski A, Sutton R, et al. Physiol Rev. 2025;105(1):209–66. 10.1152/physrev.00007.2024.

2. Bayard M, Gerayli F, Holt J. Syncope: Evaluation and Differential Diagnosis. Am Fam Physician. 2023;108(5):454–63.
3. Brignole M, Ungar A, Bartoletti A, et al. Evaluation of Guidelines in Syncope Study 2 (EGSYS-2) Group. Standardized-care pathway vs usual management of syncope patients presenting as emergencies at general hospitals. Europace. 2006;8:644–50. https://doi.org/10.1093/europace/eul098.
4. Vanbrabant P, Gillet JB, Buntinx F, et al. Incidence and outcome of first syncope in primary care: a retrospective cohort study. BMC Fam Pract. 2011;12:102. https://doi.org/10.1186/1471-2296-12-102.
5. Moya A, Sutton R, Ammirati F, et al. Guidelines for the diagnosis and management of syncope (version 2009). Eur Heart J. 2009;30:2631–71. https://doi.org/10.1093/eurheartj/ehp315.
6. Grossman SA, Babineau M, Burke L, et al. Do outcomes of near syncope parallel syncope? Am J Emerg Med. 2012;30:203.
7. Thiruganasambandamoorthy V, Stiell IG, Wells GA, et al. Outcomes in presyncope patients: a prospective cohort study. Ann Emerg Med. 2015;65:268.
8. Sun BC, Derose SF, Liang LJ et al. Predictors of 30-day serious events in older patients with syncope. Ann Emerg Med. 2009; 54:769.//Quinn JV. Syncope and presyncope: same mechanism, causes, and concern. Ann Emerg Med 2015; 65:277.
9. Mirfazaelian H, Stiell I, Masoomi R, et al. Serious outcomes among emergency department patients with presyncope: A systematic review. Acad Emerg Med. 2024 Jun;9. 10.1111/acem.14943.
10. Roncon L, Zuin M, Casazza F, et al. Impact of syncope and pre-syncope on short-term mortality in patients with acute pulmonary embolism. Eur J Intern Med. 2018;54:27–33. https://doi.org/10.1016/j.ejim.2018.04.004.
11. Sun BC, Costantino G, Barbic F, et al. Priorities for emergency department syncope research. Ann Emerg Med. 2014;64:648–55.
12. Sun BC, Thiruganasambandamoorthy V, Cruz JD. Standardized reporting guidelines for emergency department syncope riskstratification research. Acad Emerg Med. 2012;19:694–702.
13. Brignole M, Moya A, De Lange FJ et al. 2018 ESC Guidelines for the diagnosis and management of syncope. Pol Heart J (Kardiologia Polska), 76(8), 1119–98.
14. James V. Quinn. Syncope and Presyncope: Same Mechanism, Causes, and Concern. Annals of Emergency Medicine Volume 65, no. 3: March 2015.
15. Flevari P, Leftheriotis D, Kroupis C, et al. CPT levels in patients with vasovagal syncope. Int J Cardiol. 2017;230:642–5.
16. Yalta K, Yalta T, Sivri N, et al. CPT and cardiovascular disease: a review of a novel neurohormone. Int J Cardiol. 2013;167(5):1750–9.
17. Jeon J, Kim S, Kim T, et al. Association Between CPT and Six-Month Neurologic Outcomes in Patients With Moderate Traumatic Brain Injury. Front Neurol. 2022;12.

https://doi.org/10.3389/fneur.2021.749110.

18. Karatzetzou S, Tsiptsios D, Sousanidou A, et al. CPT Implementation on Stroke Prognosis. Neurol Int. 2023;15:83–99. https://doi.org/10.3390/neurolint15010008.
19. Baranowska B, Kochanowski J. CPT - a new diagnostic and prognostic biomarker in neurological and cardiovascular diseases. Neuroendocrinol Lett. 2019;40(5):207–14.
20. Schiavon L, Casarotti A, Mion MM, et al. CPT as a diagnostic and prognostic biomarker in patients admitted to Emergency Department with syncope, presyncope and vertiginous syndrome. Clin Chem Lab Med (CCLM). 2018;56(3):e72–4.
21. Lagi A, Cuomo A, Veneziani F, et al. CPT: a blood test marker of syncope. Int J Clin Pract. 2013;67. https://doi.org/10.1111/ijcp.12123.
22. Rash A, McRae M, Fatehi J, et al. Assessment of endothelin and CPT as biomarkers for vasovagal syncope. Eur J Clin Invest. 2016;46(2):141–5. 10.1111/eci.12576.
23. Juknevičienė R, Juknevičius V, Jasiūnas E, et al. Chest pain in the emergency department: From score to core-A prospective clinical study. Med (Baltim). 2022;101(29):e29579. 10.1097/MD.0000000000029579. Published 2022 Jul 22.
24. Avci II, Sahin I, Gungor B, et al. Higher CPT Levels are Associated with the Risk of Atrial Fibrillation in Patients with Rheumatic Mitral Stenosis. Acta Cardiol Sin. 2021;37(4):412–9. 10.6515/ACS.202107_37(4).20210111A.
25. Shen WK, Sheldon RS, Benditt DG, et al. 2017 ACC/AHA/HRS Guideline for the Evaluation and Management of Patients With Syncope: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Circulation. 2017;136(5):e60–122. 10.1161/CIR.0000000000000499.
26. Fedorowski A, Burri P, Struck J, et al. Novel cardiovascular biomarkers in unexplained syncopal attacks: the SYSTEMA cohort. J Intern Med. 2013;273:359–67. https://doi.org/10.1111/joim.12077.
27. Pfister R, Scholz M, Wielckens K, et al. Use of NT-proBNP in routine testing and comparison to BNP. Eur J Heart Fail. 2004;6:289–93. https://doi.org/10.1016/j.ejheart.2004.01.013.
28. Tanimoto K, Yukiiri K, Mizushige K, et al. Usefulness of brain natriuretic peptide as a marker for separating cardiac and noncardiac causes of syncope. Am J Cardiol. 2004;93:228–30. https://doi.org/10.1016/j.amjcard.2003.10.039.
29. White M, Cernacek P, Courtemanche M, et al. Impaired endothelin-1 release in tilt induced syncope. Am J Cardiol. 1998;81:460–4. https://doi.org/10.1016/S0002-9149(97)01075-3.
30. Jardine DL, Melton IC, Crozier IG, et al. Neurohormonal response to head-up tilt and its role in vasovagal syncope. Am J Cardiol. 1997;79:1302–5. https://doi.org/10.1016/S0002-9149(97)00450-9.
31. Badertscher P, Nestelberger T, de Lavallaz JDF, et al. Prohormones in the Early Diagnosis of Cardiac Syncope. J Am Heart Assoc. 2017;6(12):e006592. 10.1161/JAHA.117.006592. Published 2017 Dec 14.

Figures

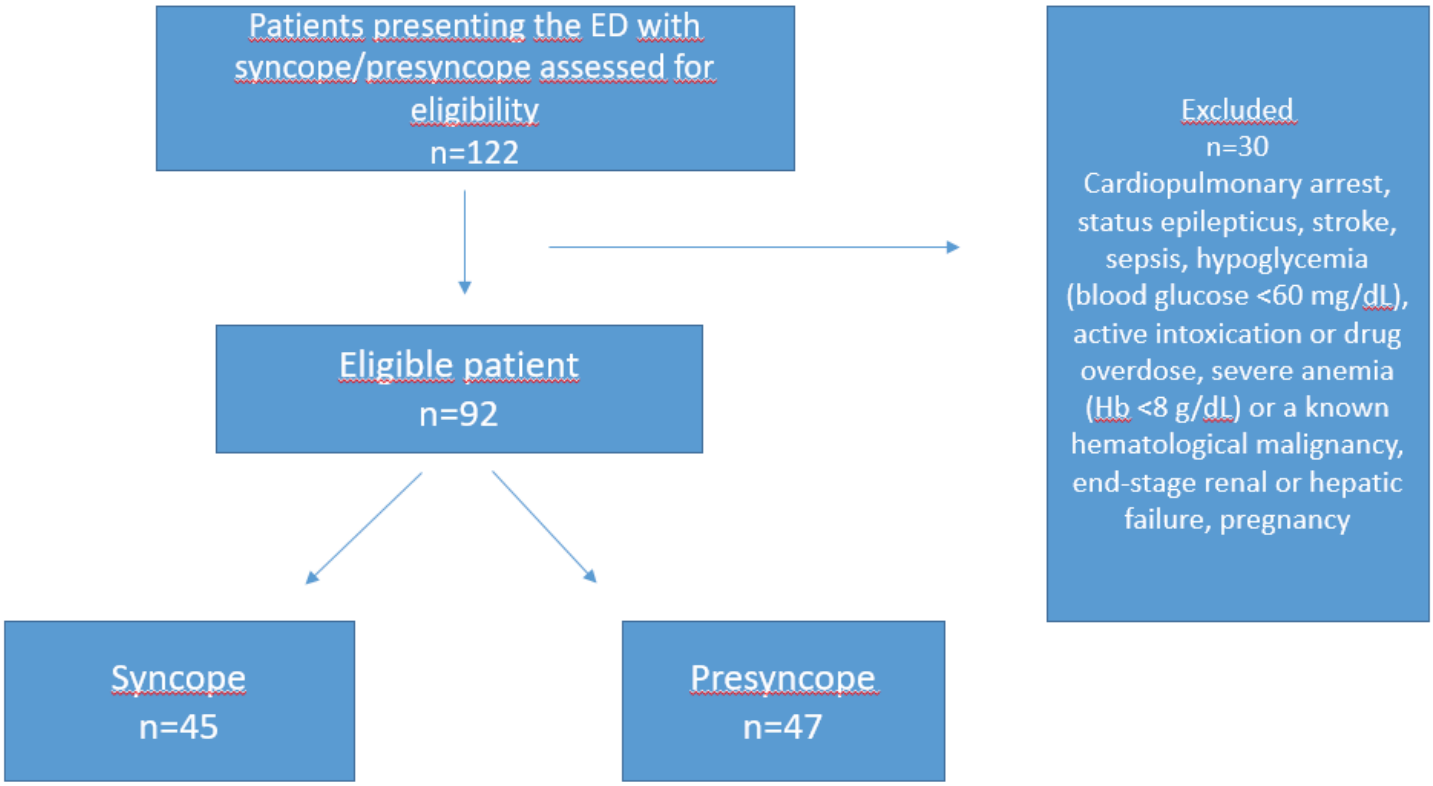


Figure 1

Flow diagram of participant selection

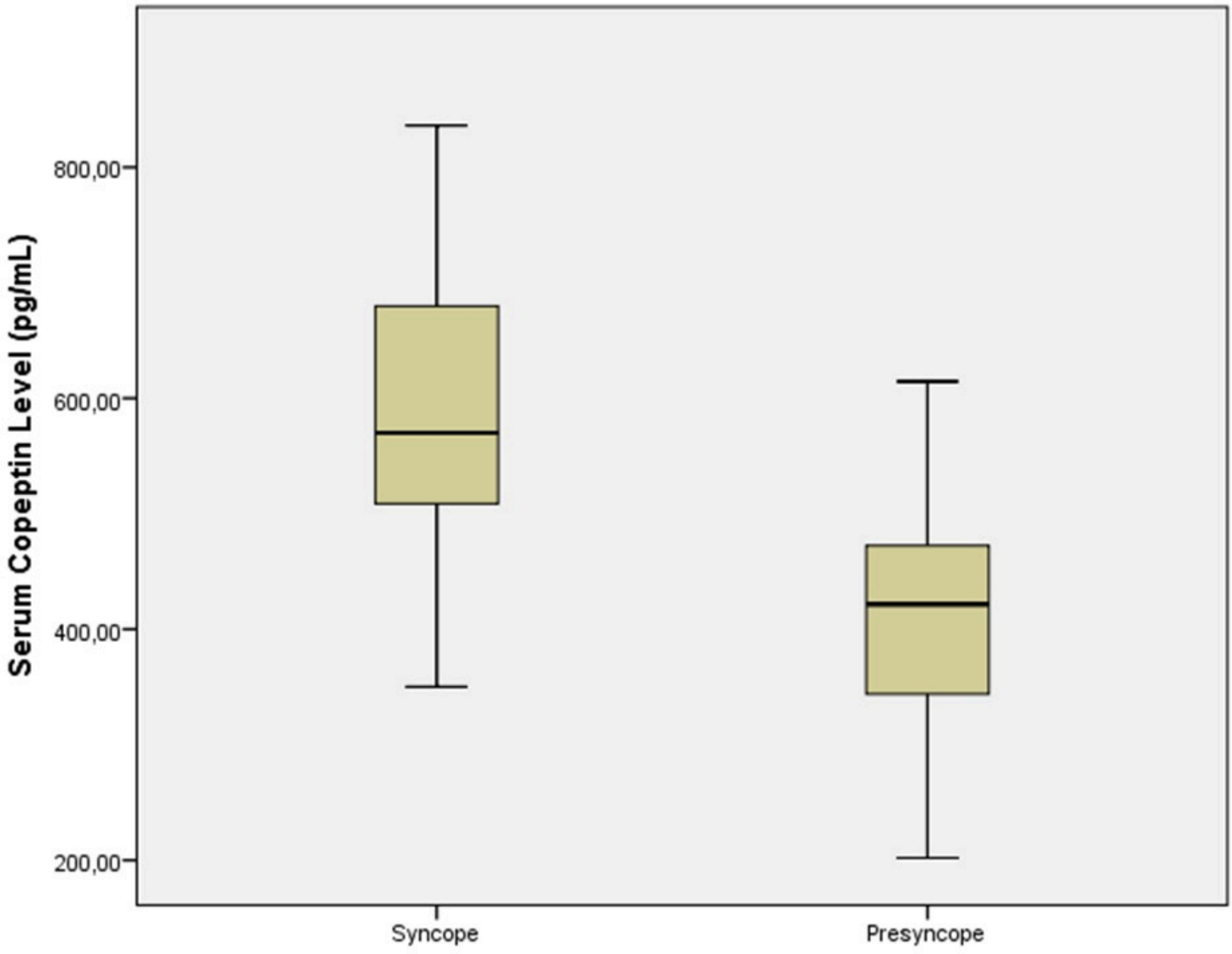


Figure 2

Relationship between serum CPT level and syncope/presyncope diagnosis

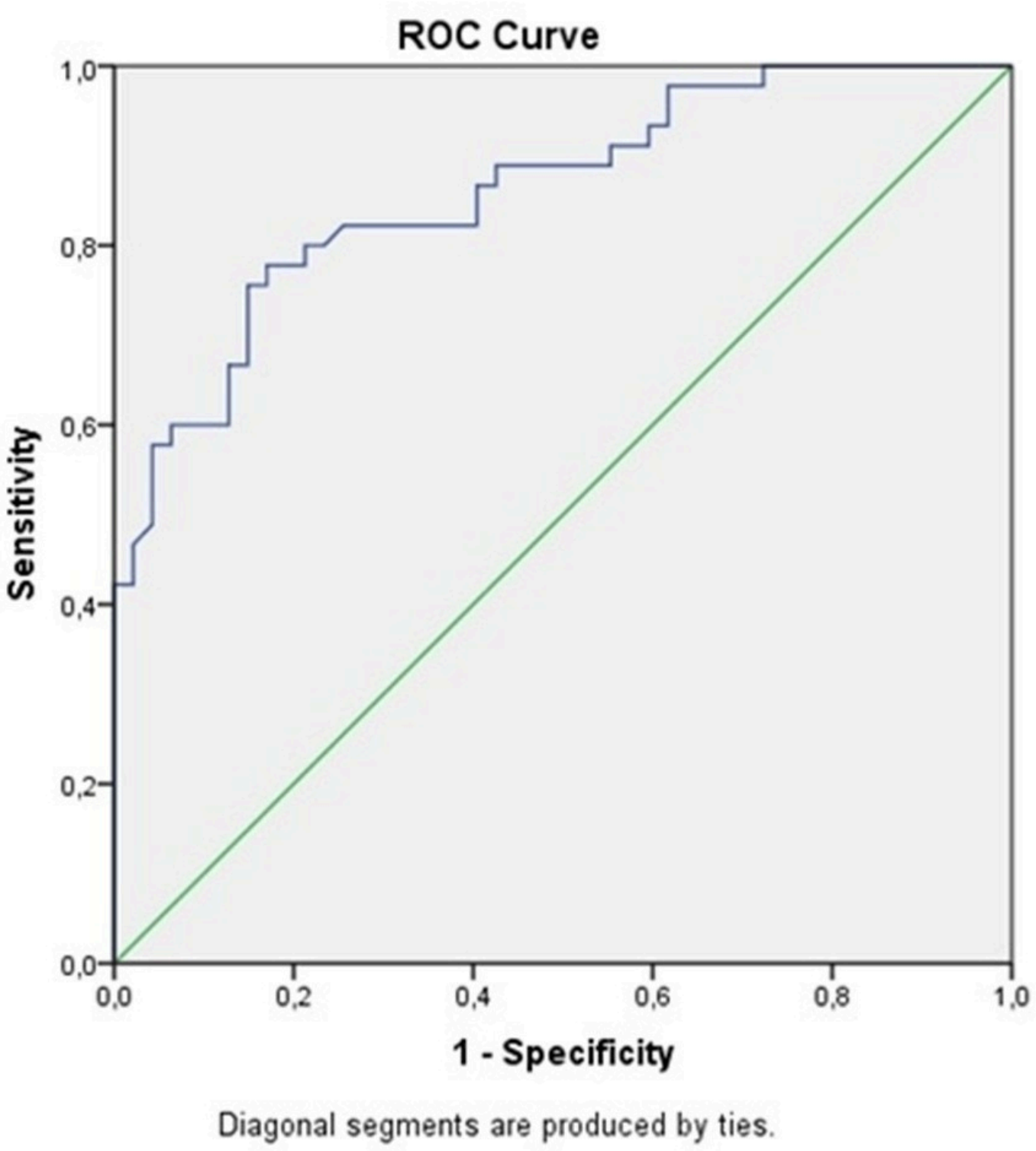


Figure 3

Receiver operating characteristic curve of serum CPT level for differentiating between syncope and presyncope

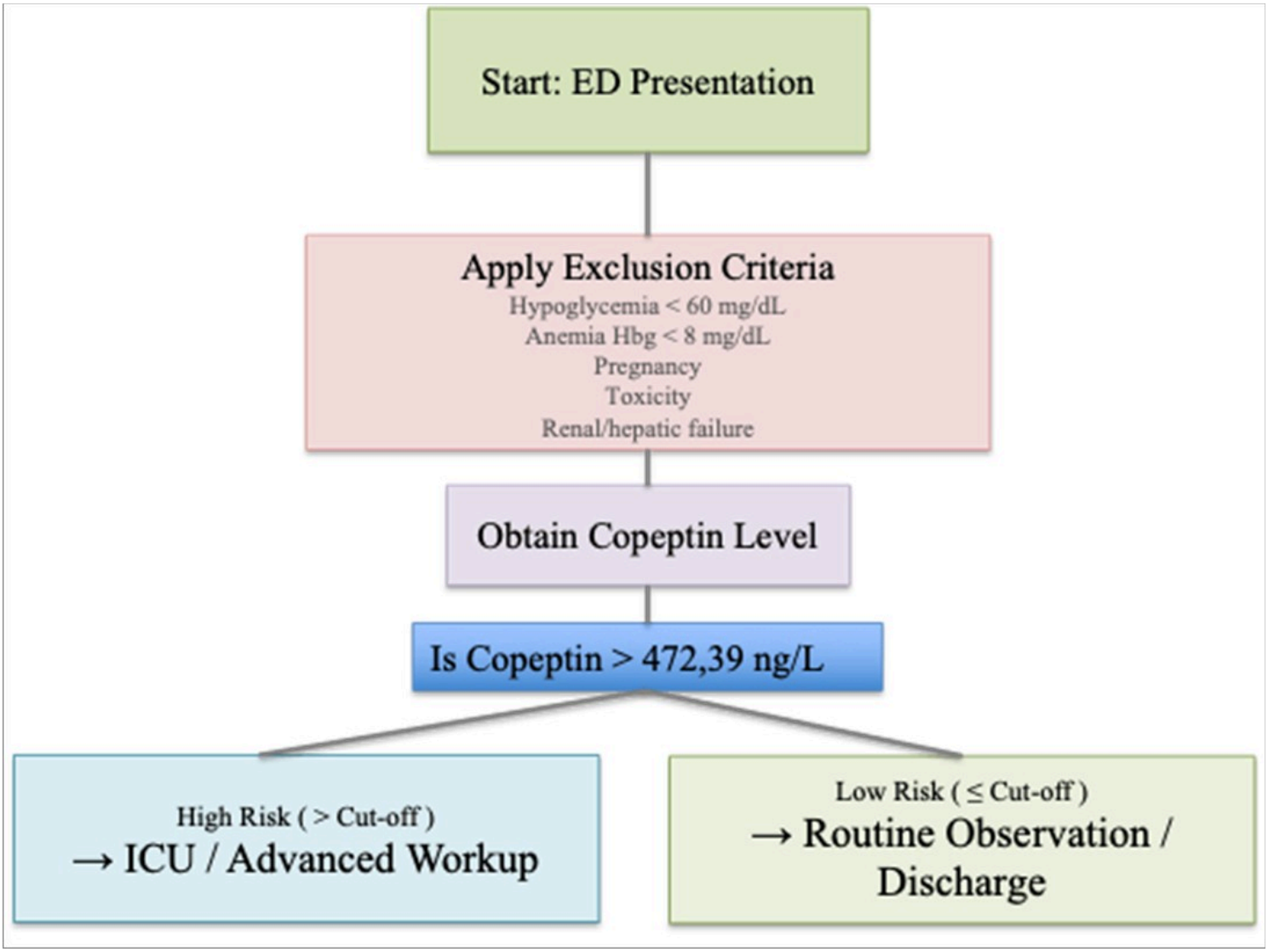


Figure 4

CPT and risk classification