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Original Article

The role of ProBNP in differentiation of cardiogenic and non-cardiogenic syncope: A diagnostic accuracy study

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Abstract

Objective: The significance of diagnosing the root reason for syncope and taking the required preventive or treatment measures cannot be overlooked when it comes to outcome prediction. This study endeavors to examine the role of proBNP in differentiating cardiogenic and non-cardiogenic syncope in patients presenting to the emergency department (ED).

Methods: We prospectively performed a cross-sectional study on patients presenting with acute syncope. All the patients for this investigation were followed up until the definite cause of their syncope (cardiac or non-cardiac) was diagnosed and the screening performance characteristics of proBNP in differentiation of cardiogenic and non-cardiogenic syncope were evaluated.

Results: Three hundred patients with syncope were studied (64.7% male). In the end, the cause of syncope was determined to be cardiogenic in 133 cases (44.3%). The area under the ROC curve of proBNP in the differentiation of cardiogenic syncope from non-cardiogenic was estimated to be 78.9 (95% CI: 73.5 – 84.3). The optimal cut-off point for proBNP in this regard was 143.5 pg/mL point. Sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios of proBNP in the mentioned cut-off point were 75.39% (95% CI: 67.61–82.73), 75.44% (95% CI: 68.07–81.62), 71.12% (95% CI: 62.82–78.26), 79.74% (95% CI: 72.46–85.54), 2.46 (95% CI: 1.86–3.25), and 0.25 (95% CI: 0.18–0.34), respectively.

Conclusion: The accuracy of proBNP in differentiation of cardiogenic and non-cardiogenic syncope is fair. ProBNP concentration equals to or higher than 143.5 pg/mL can differentiate cardiogenic syncope from non-cardiogenic with 75% sensitivity and 76% specificity. It seems that its use for this purpose should be considered with caution and along with other tools.

Keywords: Syncope, Causality, Pro-brain natriuretic peptide, Heart failure, Emergency medicine, Diagnosis

Introduction

Syncope is an abrupt albeit temporary loss of consciousness and loss of skeletal muscle tone. It results from reduced cerebral blood flow (1). The duration of syncope varies from a few seconds to a few minutes and the patient regains full consciousness automatically (2). About one third of people experience syncope at least once during their lifetime and 3%-6% of visits to hospitals happen following syncope (3,4). Etiology of syncope is classified into cardiac and non-cardiac types. The most important stage of diagnosis and treatment is distinguishing cardiac from non-cardiac causes based on the standard and international criteria of dealing with these patients (1,2).

About 11% of patients presenting with syncope experience dangerous outcomes, which threaten the life of the patient or decrease their quality of life (5). The risk of mortality and undesirable outcomes is much higher in cardiogenic syncope (6-8). Therefore, rapid diagnosis of

etiology and determining the prognosis of the patient with syncope is of great help in decreasing their mortality and improving their outcome (9). Numerous criteria have been introduced for determining prognosis and identifying high-risk patients among those with syncope until now. Among the most important of which are OESIL system, San Francisco, Boston, ROSE, and Canadian syncope risk score (10-13). In addition to these clinical decision rules, a series of biomarkers such as proBNP have also been considered for this purpose. Of course, the accuracy of these biomarkers and their routine use in routine practice should be further studied (14,15). Considering the aforementioned points, this paper aims at evaluating the role of proBNP as a biomarker for differentiating cardiogenic syncope from non-cardiogenic ones.

Methods

Prospectively, we carried out a cross-sectional study on all consecutive patients presenting to the emergency department (ED) of Imam Hossein and Shohadaye Tajrish hospitals, Tehran, Iran, from October 2018 to October 2019 following syncope. The convenience sampling method was used for patient selection. Patients were followed up until the definite cause of their syncope was diagnosed, and the screening performance characteristics of proBNP for differentiating cardiogenic and non-cardiogenic syncope were evaluated. The researchers provided the cost of proBNP tests, and no additional charge was inflicted on the patients. Besides, verbal consent was granted from all patients.

Patients under 18 years of age, those who were not able to give informed consent, patients whose loss of consciousness happened due to reasons other than syncope, including vertigo, coma, hypoglycemia, head trauma, and brain stroke, those with continuous change in psychological status, loss to follow-up, pregnancy, and history of drug or alcohol abuse, patients who did not give a clear history of syncope or near syncope, and patients with suspected poisoning were not included in the study. In addition, if the cause of the syncope remained unclear after all diagnostic measures and screening during the one-month follow-up the patient would be excluded.

To collect the required data, a checklist was used. It included demographic variables (age and sex), vital signs (heart rate, diastolic and systolic blood pressure, and respiratory rate), laboratory findings on admission (level of creatinine, urea, hematocrit, and troponin), past medical history, prodromal and vasovagal symptoms before syncope, electrocardiography findings, and proBNP levels of the patients admitted via the ED. Evaluation of patients' electrocardiogram was done by a cardiologist who did not know about the study and presence of changes in electrocardiogram including bradycardia, AV block, intraventricular conduction disorders, tachyarrhythmia, Brugada syndrome, long QT interval, ventricular hypertrophy, and acute coronary syndrome. A senior emergency medicine resident, whose work and performance were supervised by an emergency medicine attending physician, handled the data collection procedures and was in charge of the follow-up of patients. Since the laboratory kit used in the present study (Immulite 2000 manufactured by Siemens) showed measures less than 20 pg/mL as < 20 and did not show a specific number, all measures less than 20 were considered as 20 pg/mL.

Blood samples were drawn from the middle cubital vein of all patients in the first hour of their admission to the ED and sent to the laboratory for determining the level of proBNP. Based on the protocol of the approach to patients with syncope in the mentioned ED, after taking the initial measures and ruling out any life threatening causes, if we were unable to identify the cause of syncope, the patient would be referred to a cardiologist and/or neurologist, based on the opinion of the emergency medicine specialist, for undergoing complementary screening tests (diagnostic tests such as echocardiography, tilt test, color doppler sonography of carotid arteries, electroencephalography, etc) as an outpatient or an inpatient (based on the opinion of the cardiologist or neurologist). The emergency medicine resident was responsible for following the patient until the completion of screening tests and the neurologist or cardiologist reached a final diagnosis regarding the cause of syncope for a maximum of 1 month. In the present study, the reference of the researchers for the cause of syncope was the results of screening tests and the final opinion of the cardiologist and neurologist evaluating the patient. In cases of disagreement regarding the source of syncope, a second specialist was consulted. The cardiologist and neurologist in charge of the patient were blind to the results of proBNP level of the patient.

The data analysis was guided by SPSS software (version 18). Variables were reported as mean ± standard deviation (SD) or frequency and percentage. The final diagnosis made by the cardiologist or neurologist after performing accurate diagnostic tests regarding the cause of syncope was considered the gold standard. In addition, to choose the best NT-proBNP cut-off using the area under the receiver operating characteristic (ROC) curve; sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios of proBNP in the differentiation of cardiogenic and non-cardiogenic syncope were also evaluated and reported with 95% confidence interval (CI). Additionally, if the p-value is lower than 0.05, it is considered statistically significant. Values for the area under the curve were interpreted as follows: 90-100 excellent; 80-90 good; 70-80 fair; 60-70 poor, and 50-60 fail.

Results

Three hundred patients with a mean age of 52.6 ± 38.1 (18–90) years were studied (64.7% male). In the end, the

cause of syncope was determined to be cardiogenic in 133 (44.3%) cases and non-cardiogenic in 167 (55.7%) cases. Table 1 shows the comparison of baseline features of patients based on the cause of syncope. It is important to mention that patients with cardiogenic syncope indicated a greater mean age ($P<0.001$), tremendous rate of cardiovascular disease history ($P<0.001$), and less prodromal ($P=0.036$) and vasovagal ($P<0.001$) symptoms. In addition, electrocardiogram findings of these patients indicated longer QRS ($P<0.001$) and QT ($P<0.001$) intervals, a higher frequency of left bundle branch block (LBBB) ($P<0.001$), and evidence of left ventricular hypertrophy (LVH) ($P<0.009$). The mean of proBNP level among patients with cardiogenic syncope was 2590.6 ± 6517.70, while the level was 225.93 ± 514.83 among patients with non-cardiogenic syncope. Table 2 compares the frequency of different proBNP ranges between the two groups.

Area under the ROC curve of proBNP in distinguishing cardiogenic and non- cardiogenic syncope was calculated to be 78.9 (95% CI: 73.5–84.3) (Figure 1). Therefore, the excellent cut-off point for proBNP in this regard was 143.5 pg/mL. Sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios of proBNP in differentiation of cardiac and non-cardiac syncope in the mentioned cut-off point were 75.39% (95% CI: 67.61–82.73), 75.44% (95% CI: 68.07–81.62), 71.12% (95% CI: 62.82–78.26), 79.74% (95% CI: 72.46–85.54), 2.46 (95% CI: 1.86–3.25), and 0.25 (95% CI: 0.18–0.34), respectively.

Discussion

As this research demonstrated, proBNP biomarker has fair accuracy in differentiation of cardiogenic and non-cardiogenic syncope. ProBNP concentration equal to or higher than 143.5 pg/mL can differentiate cardiogenic syncope from non-cardiogenic with 75% sensitivity and 76% specificity. It seems that its use for this purpose should be considered with caution and along with other tools.

A study by Pfister et al showed that proBNP could be helpful in the diagnosis of cardiogenic syncope in patients for the first time. In patients with arrhythmia and those with cardiac or cardiopulmonary cause, the level of proBNP was significantly greater than patients with non-cardiogenic syncope. In that study, proBNP had high sensitivity and negative predictive value for cardiac diseases as a stand-alone parameter and was a better predictor compared to clinical symptoms and electrocardiogram (16). Tanimoto et al also carried out a retrospective study on 148 patients with a history of syncope who had been admitted to a hospital in Kagawa (Japan) during a 4-year period. These researchers found that a BNP concentration higher than 40 pg/mL could differentiate cardiogenic and non-cardiogenic syncope (82% sensitivity, and 92%

Table 1. Comparing the baseline characteristics of studied cases based on the cause of syncope

Variable	Cause of syncope		*P* value
	Non-cardiac (n = 167)	Cardiac (n = 133)	
Age (y)			
Mean ± SD	49.38 ± 18.85	65.18 ± 15.7	<0.001
Gender			
Male	115 (59.3)	79 (40.7)	0.088
Female	52 (49.1)	54 (50.9)	
Vital sign (presenting to ED)			
SBP (mm Hg)	126.86 ± 28.26	138.38 ± 28.95	0.001
DBP (mm Hg)	78.5 ± 14.86	83.20 ± 14.83	0.003
PR (/minute)	80.73 ± 11.97	82.92 ± 23.52	0.296
RR (/minute)	17.20 ± 1.54	17.62 ± 1.85	0.034
Symptom			
Prodromal	43 (25.7)	21 (15.8)	0.036
Vasovagal	31 (18.6)	13 (9.8)	0.033
Background disease			
Cardiac	16 (2.9)	57 (42.9)	<0.001
Vascular	41 (24.6)	92 (69.2)	<0.001
ECG findings			
QRS (ms)	81.56 ± 8.77	90.23 ± 19.63	<0.001
Axis (degree)	27.90 ± 28.59	14.25 ± 50.92	0.004
QT interval (ms)	414.85 ± 30.94	429.10 ± 34.42	<0.001
LBBB	2 (1.2)	15 (11.3)	<0.001
LVH signs	20 (12.0)	31 (23.3)	0.009
Laboratory findings			
Hematocrit (%)	40.12 ± 5.25	38.69 ± 5.70	0.025
BUN (mg/dL)	24.70 ± 14.01	33.06 ± 22.77	<0.001
Creatinine (mg/dL)	1.14 ± 0.30	1.43 ± 1.01	0.001
ProBNP (pg/mL)	225.93 ± 514.83	2590.6 ± 6517.70	<0.001
Elevated troponin	4 (2.4)	26 (19.5)	<0.001

Data are presented as mean ± standard deviation (SD) or frequency (%).
SBP: systolic blood pressure; DBP: diastolic blood pressure; PR: pulse rate; RR: respiratory rate; msec: millisecond; BUN: blood urea nitrogen; BNP: brain natriuretic peptide; ED: emergency department; LBBB: left bundle branch block; LVH: left ventricular hypertrophy.

Table 2. Comparing the frequency of different proBNP ranges between patients with cardiogenic and non-cardiogenic syncope

ProBNP level (pg/mL)	Source of syncope		*P* value
	Non-cardiogenic (n = 167)	Cardiogenic (n = 133)	
<50	133 (79.7)	27 (20.3)	<0.001
50-150	130 (78.0)	29 (22.0)	
150-500	80 (48.1)	69 (51.9)	
500-1000	37 (21.9)	103 (78.1)	
1000-5000	34 (20.5)	106 (79.5)	
≥ 50000	0 (0.0)	167 (100.0)	

Data are presented as No. (%).

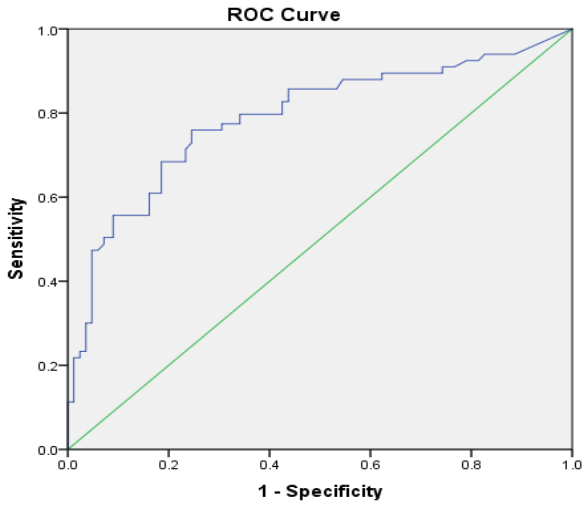

Figure 1. Area under the receiver operating characteristic (ROC) curve of proBNP in differentiating cardiogenic and non-cardiogenic syncope ($P<0.001$).

specificity) (17). In addition, Pfister et al first examined 61 patients and then 161 patients who were admitted due to syncope. It was revealed that proBNP concentrations over 156 pg/mL would predict a cardiac cause for syncope with 89.7% sensitivity and 51.8% specificity (18,19). Another study was performed with the aim of risk assessment in patients with syncope presenting to the ED, which reported three notable findings. First, the proBNP concentration was found to be statistically significantly higher in patients with cardiogenic syncope, and had fair to high accuracy in diagnosing cardiogenic syncope. Second, if used as a tool for triage of patients in the study population, which were patients aged above 45 years old with syncope who presented to the ED, concentrations of proBNP, hs-cTnI, hs-cTnT, and BNP would lead to precluding cardiogenic syncope in about one third of the patients with 95% sensitivity and 95% specificity. Third, the above-mentioned laboratory parameters were extremely accurate in predicting both short-term and long-term mortality and had better performance, compared to a mixture of clinical variables or some of the scoring systems for estimating risk of syncope. They concluded that the clinical application of the biomarkers is probably more effective in the group of patients whose diagnosis has remained unclear after standard diagnostic processes (20). In harmony with previous studies in other countries, in the present study it was shown that proBNP is a sensitive marker for patients with cardiogenic syncope and particularly for patients who are in need of cardiovascular treatment interventions. However, it is not clear if proBNP can effectively indicate a cardiac cause for syncope as an independent parameter or not.

In the present study, the concentration of proBNP was 2590.07 ± 6517.7 in patients with cardiogenic syncope and 225.93 ± 514.83 in patients with non- cardiogenic syncope. As it is evident, the level of proBNP is significantly greater in the setting of cardiac syncope. It should be noted that proBNP evaluation is widely available in both ED and other hospital wards. The time required for testing is short and it takes around 18 minutes. The cost of proBNP evaluation is not higher than other tests (such as c-reactive protein, troponin, and d-dimer), which are routinely used in ED.

It seems that determining proBNP concentration in ED before performing additional studies could be helpful in categorizing syncope types, which may be highly effective in making a final diagnosis.

Limitations of the study

Despite performing all clinical, laboratory, and imaging procedures, determining the definitive cause of syncope is sometimes associated with problems, especially in young patients without any underlying illnesses; and in these cases, the in-charge physicians treat the patient based on evidence and their experience. This may be a confounding factor affecting the accuracy calculated for the tools used in order to determine the cause of syncope.

Conclusion

As the results of this research demonstrated, proBNP has fair accuracy in the differentiation of cardiogenic and non-cardiogenic syncope. ProBNP concentration equal to or higher than 143.5 pg/mL can differentiate cardiogenic syncope from non- cardiogenic with 75% sensitivity and 76% specificity. It seems that its use for this purpose should be considered with caution and along with other tools.

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Authors' contributions

Study Design: SSa and AA; Data gathering: ZSK, MAC, RKO, AG, MPM, and SSh; Analysis: SSa; Interpretation of results: SSa, AA, MAC, AG, and ZSK; Drafting: SSa, SSh, AG; Critically revised: All authors.

Ethical issues

Research ethics committee at Shahid Beheshti University of Medical Science approved the research protocols (Research ethics code: IR.SBMU.MSP.REC.1397.432) and the researchers adhered to the ethical principles of declaration of Helsinki and confidentiality of patients' information.

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