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Diagnostic value of cardiac troponin I and N-terminal pro-B-Type Natriuretic Peptide in cardiac syncope

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ABSTRACT

Objective: The study aims to evaluate the diagnostic accuracy of Cardiac Troponin I(cTnI) and N-terminal pro-B-Type Natriuretic Peptide (NT-proBNP) for identifying patients with cardiac syncope.
Methods: This is a prospective, single-center cohort study of patients presenting with syncope hospitalized from June 21,2018 to May 30, 2019. The Evaluation of Guidelines in Syncope Study (EGSYS), a syncope-specific diagnostic score, was used for diagnostic comparator.
Results: A total of 118 patients were enrolled (mean age: 69.1 ± 12.3 years, 40% female). Compared to patients with reflex, orthostatic, or unexplained syncope, patients adjudicated to have cardiac syncope showed significantly higher cTnI and NT-proBNP plasma concentrations ($p < 0.001$ for each comparison). The area under the curve (AUC) of cTnI and NT-proBNP were moderate-to-good [0.77–0.78; 95% confidence interval (CI) 0.66–0.86], and was similar to that of EGSYS (0.71, 95%CI 0.60–0.80). Incorporation of cTnI and/or NT-proBNP into the existing EGSYS score significantly improved the diagnostic accuracy (EGSYS + cTnI: AUC 0.83; 95%CI 0.74–0.90; EGSYS + NT-proBNP: AUC 0.81; 95%CI 0.71–0.89; EGSYS + cTnI + NT-proBNP: AUC 0.83; 95%CI 0.73–0.90).
Conclusions: The cTnI and NT-proBNP levels were significantly higher in patients adjudicated to have cardiac syncope and the addition of both biomarkers to the EGSYS score significantly improved the diagnostic value for cardiac syncope.

1. Introduction

Syncope is a common clinical presentation defined as a transient loss of consciousness due to cerebral hypoperfusion (Brignole et al., 2018). The term cardiac syncope refers to syncope caused by bradycardia, tachycardia, or hypotension due to low cardiac index, blood flow obstruction, vasodilatation, or acute vascular dissection (Shen et al., 2017). The 2017 ACC/AHA/HRS Guideline have reported cardiac syncope as the second commonest cause of syncope with an estimated prevalence of 9% (Shen et al., 2017). In contrast to reflex syncope, syncope with cardiac causes is associated with a higher risk of hospitalization and death.

Cardiac troponin I (cTnI) and N-Terminal Pro-B-Type natriuretic peptide (NT-proBNP) are commonly used in the diagnosis and the prognosis evaluation of cardiac disease. Both biomarkers have recently been proposed for identifying patients with syncope at risk for adverse events. Probst et al. (2020) reported high-sensitivity cardiac troponin T and NT-proBNP showed a high sensitivity for excluding death and serious cardiac outcomes in older adults with syncope of cardiac cause.

The Evaluation of Guidelines in Syncope Study (EGSYS) was a diagnostic score for cardiac syncope and validated in several studies (Probst et al., 2020; Ungar et al., 2010; Kariman et al., 2015; Kayayurt et al., 2012; Gomes et al., 2016), which was selected as a diagnostic comparator (Del Rosso et al., 2008).

We performed a prospective cohort study to examine the diagnostic accuracy of cTnI and NT-proBNP to identify patients with cardiac syncope and tested the hypothesis that their incorporation into EGSYS can further improve risk stratification.

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2. Methods

2.1. Study setting and population

This is a prospective, single-center cohort study including patients presenting with syncope hospitalized from June 21, 2018 to May 30, 2019. The study site was at the Second Hospital of Tianjin Medical University, which is a large community hospital and syncope center.

The inclusion criteria were patients aged 18 years or older with a hospitalization due to syncope. Syncope was defined as transient loss of consciousness due to cerebral hypoperfusion, characterized by a rapid onset, short duration, and spontaneous complete recovery. The exclusion criteria were: 1) syncope due to intoxication, seizure, stroke, transient ischemic attack, head trauma, or hypoglycemia, 2) new or worsening confusion, or 3) inability to obtain informed consent from the patient or a legally authorized representative. The primary study endpoint was the diagnostic accuracy of cTnI and NT-proBNP. The definitive diagnosis of cardiac syncope referred to the 2017 ESC ST segment Elevation Myocardial Infarction guideline (Ibanez et al., 2017). Secondary study endpoint defined as a composite of death.

Our study was a part of Chinese prospective multicenter registry of syncope patients (Trial Registration No. ChiCTR1900024190), which was carried out according to the principles of the Declaration of Helsinki and approved by the respective Ethics Committees. All patients provided informed consent before participation.

2.2. Data collection

All patients were evaluated including a detail history, physical examination, cardiac biomarker testing, and 12-lead ECG testing. Screening for eligible patients was performed using standard definitions and directly questioned patients about symptoms associated with the syncopal episode. Additional diagnostic tests such as transthoracic echocardiography and coronary arteriography were performed at the discretion of the physicians (Probst et al., 2020). Troponin was determined by double antibody sandwich immunology. The stata by Beckman Access chemiluminescence analysis has a reference 99th percentile cutoff limit of 30 ng/L for cTnI. The NT-proBNP assay used was chemiluminescence analysis, with recommended use of a 125 ng/L lower limit of normal for patients under 75 years and 450 ng/L for patients over 75 years. The EGSYS included 5 predictors: Abnormal ECG and/or heart disease (3 points), palpitations before syncope (4 points), syncope during effort (3 points) or in supine position (2 points), autonomic prodromes (−1 points) and predisposing and/or precipitating factors (−1). A score $\geq$3 identified cardiac syncope (Del Rosso et al., 2008).

2.3. Statistical analysis

The categorical variables were compared using the Pearson Chi-square test or Fisher's exact test and reported as the frequency with proportion. Nonparametric techniques were used to compare continuous variables, reported as the medians (with the interquartile range [IQR]), as appropriate. Wilcoxon 2-sample test was used to assess the differences in the plasmatic concentration variation of cTnI and NT-proBNP between the cardiac and control group. The area under the ROC(AUC) curve with the 95% confidence interval was calculated to evaluate the diagnostic accuracy. A p-value <0.05 was considered statistically significant. The cut-off value was corresponding to the maximum of the Yoden index. Comparisons of AUCs were performed according to DeLong (DeLong et al., 1998). Statistical analyses were performed with the use of SPSS, version 24.0 (IBM, Munich, Germany).

3. Results

A total of 141 patients presenting with syncope to the study hospital between June 2018 and May 2019 were screened. Of these, 23 (16.3%) were excluded because of no availability of biomarker data or the EGSYS score could not be calculated. Subsequently, 118 patients with complete data were used for analysis.

3.1. Characteristics of the patients

The baseline characteristics of the study cohort are detailed in Table 1. The mean age of the study sample was 69.1 ± 12.3 years, and 40% were female. There were no significant differences in age, gender, blood pressure or heart rate between cardiac syncope when compared to non-cardiac or unexplained syncope groups. Patients with a diagnosis of cardiac syncope were more likely to have syncope during supine posture. Cardiac syncope patients were more likely to have undiagnosed cardiovascular disease. In addition, the levels of creatinine kinase -MB, glucose, aspartate Aminotransferase were significantly higher in patients with cardiac syncope.

3.2. Concentrations of cTnI, NT-proBNP and syncope etiology

Compared to patients with reflex, orthostatic, or unexplained syncope, cTnI and NT-proBNP plasma concentrations were significantly higher in patients adjudicated to have cardiac syncope (Fig. 1A and Fig. 1B, $p < 0.001$ for each comparison).

3.3. Diagnostic value for cardiac syncope

The diagnostic values of the clinical scores and biomarkers alone and in combination for cardiac syncope are presented in Table 2. The ROC curves are shown in the Fig. 2 with AUCs values shown in Table 3 and Fig. 1C. The AUCs of cTnI and NT-proBNP were moderate-to-good (all AUCs 0.77–0.78; 95% confidence interval (CI) 0.66–0.86), similar to that of EGSYS (AUC 0.71, 95%CI 0.60–0.80). Incorporation of cTnI and/or NT-proBNP significantly improved the diagnostic accuracy of the EGSYS score (EGSYS + cTnI: AUC 0.83; 95%CI 0.74–0.90; EGSYS + NT-proBNP: AUC 0.81; 95%CI 0.71–0.89; EGSYS + cTnI + NT-proBNP: AUC 0.83; 95%CI 0.73–0.90).

3.4. The optimal cTnI and NT-proBNP cut-offs

When the cut-off value was 5 ng/L, the cTnI had a sensitivity of 77.5% (95% CI 61.5–89.2) and specificity of 68.9% (95% CI 53.4–81.8). When the cut-off value was 133 ng/L, the NT-proBNP had a sensitivity of 89.2% (95% CI 74.6–97.0) and specificity of 59.5% (95% CI 43.3–74.4). We were verified the EGSYS as well, which had a sensitivity of 80.0% (95% CI 64.4–90.9) and specificity of 62.2% (95% CI 46.5–76.2).

4. Discussion

The main findings of this study are that: 1) cTnI and NT-proBNP levels were significantly higher in patients adjudicated to have cardiac syncope than in those with other etiologies. 2) both biomarkers provided moderate-to-high diagnostic accuracy for cardiac syncope, which was similar to that of EGSYS scores, and 3) incorporation of both biomarkers to the EGSYS score significantly improved its predictive performance.

Compared with adults who presented with syncope to the emergency department and discharged on the same day, inpatients tended to show more severe symptoms relevant to syncope, with higher incidence of serious adverse outcomes. Therefore, there is a need to devise clinical tools that can accurately identify inpatients with cardiac syncope. The biomarkers, cTnI and NT-proBNP, are previously performed for the presence and severity of cardiac disease and for the risk stratification after syncope (Probst et al., 2020; Gibson et al., 2018; Reed et al., 2007, 2011). In recent years, the usefulness of cTn and NT-proBNP has been established in the context of syncope diagnosis, but the results were inconsistent (Christ et al., 2015; Costantino et al., 2014; du Fay de Lavallaz et al., 2019). Our study showed that cTnI and NT-proBNP levels

Table 1
Characteristics of the patients with syncope.

	Cardiac(N = 40)	Non Cardiac(n = 45)	Unexplained(N = 33)	P value
Age(years)	69.1 ± 12.3	68.8 ± 12.5	67.2 ± 12.5	0.844
Female sex	16(40.0)	22(48.9)	17(51.5)	0.573
Systolic BP, mm Hg	128.2 ± 27.0	136.0 ± 21.9	128.7 ± 24.7	0.270
Heart rate, beats/min	73.3 ± 33.1	74.8 ± 19.3	70.9 ± 15.3	0.689
Characteristics of the syncope				
Syncope frequency, n (%)				
1	22(55.0)	18(40.0)	22(66.7)	0.054
2 or 3	11(27.5)	15(33.3)	4(12.1)	0.098
≥4	7(17.5)	12(26.7)	7(21.2)	0.422
Position of the syncope, n (%)				
While standing	16(40.0)	20(44.4)	16(48.5)	0.766
While sitting	17(42.5)	24(53.3)	13(39.4)	0.417
While lying	8(20.0)	0	4(12.1)	0.003
Orthostatic	0	10(22.2)	0	<0.001
Exertion	1(2.5)	3(6.7)	7(21.2)	0.026
With incentives	12(30.0)	25(55.6)	7(21.2)	0.004
Comorbidities, n (%)				
Hypotension	22(55.0)	25(55.6)	16(48.5)	0.800
Diabetes	8(20.0)	8(17.8)	6(18.2)	0.963
Coronary artery disease	6(15.0)	13(28.9)	17(51.5)	0.003
Arrhythmia	12(30.0)	10(22.2)	11(33.3)	0.524
Congestive heart failure	2(5.0)	1(2.2)	2(6.1)	0.628
Cerebrovascular disease	6(15.0)	6(13.3)	6(18.2)	0.840
Laboratory parameters, median (IQR)				
cTnI, ng/L	38.5(6.3–261.0)	2.0(1.0–11.0)	4.0(2.0–14.0)	<0.001
NT-proBNP, ng/L	575.0(240.5–2031.0)	99.2(49.3–440.8)	494.0(84.3–1527.8)	<0.001
D-dimer, ng/mL	643.4(291.8–1162.3)	456(231.52–1035.41)	723.1(309.5–1566.3)	0.395
CK, U/L	63.5(51.3–213.5)	68.4(49.1–97.5)	68.0(35.0–131.0)	0.806
CK-MB, U/L	14.0(9.0–33.0)	10.8(5.0–15.4)	12.0(8.0–17.0)	0.039
Creatinine, ummol/L	73.8(61.5–92.8)	74.3(57.5–85.6)	71.7(58.6–89.8)	0.721
Glucose, mmol/L	7.4(5.8–9.6)	5.9(5.0–7.1)	6.7(5.0–8.3)	0.009
ALT, U/L	21.1(14.0–34.2)	17.7(11.0–26.7)	15.3(9.4–23.7)	0.053
AST, U/L	24.5(14.8–67.7)	17.1(14.8–21.3)	17.7(13.3–22.9)	0.032
Hemoglobin, g/L	132.0(115.5–137.0)	132.5(118.3–144.8)	128.0(113.0–143.5)	0.754
Hematocrit value, %	38.6(35.3–40.6)	39.8(35.1–42.0)	38.6(34.5–42.4)	0.677

IQR = interquartile range, cTnI = Cardiac Troponin I, NT-proBNP = N-Terminal Pro-B-Type Natriuretic Peptide, CK=Creatine kinase, CK-MB=Creatine kinase -MB, ALT = Alanine aminotransferase, AST = Aspartate Aminotransferase.

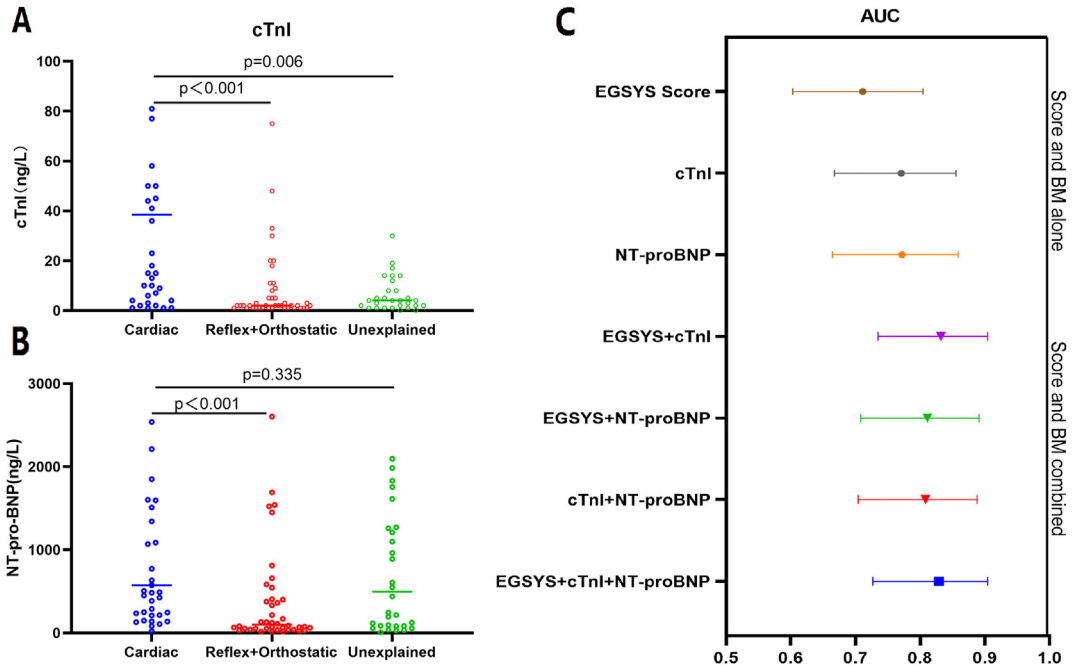

Fig. 1. (A and B). Scatterplots with median values of cTnI (A) and NT-proBNP (B) plasma levels in different types of syncope (cardiac syncope n = 40, reflex or orthostatic syncope n = 45, unexplained syncope n = 33). C. forest plot representing the AUC of the EGSYS scores, cTnI, NT-proBNP alone and biomarkers and combined. Points represent the AUC, Whiskers represent 95% confidence interval. BM =Biomarker.

Table 2
Diagnostic values of clinical scores and biomarkers alone and in combination.

	Sensitivity (95%CI)	Specificity (95%CI)	LR + (95%CI)	LR-(95%CI)	PPV (95%CI)	NPV (95%CI)
EGSYS Score	80.00(64.4–90.9)	62.22(46.5–76.2)	2.12(1.4–3.2)	0.32(0.2–0.6)	65.3(55.6–73.9)	77.8(64.4–87.1)
cTnI>5 ng/L	77.50(61.5–89.2)	68.89(53.4–81.8)	2.49(1.6–4.0)	0.33(0.2–0.6)	68.9(58.2–77.9)	77.5(65.2–86.3)
NT-proBNP>133 ng/L	89.19(74.6–97.0)	59.52(43.3–74.4)	2.2(1.5–3.2)	0.18(0.07–0.5)	66.0(56.9–74.0)	86.2(70.6–94.2)
EGSYS + cTnI	70.00(53.5–83.4)	84.44(70.5–93.5)	4.50(2.2–9.2)	0.36(0.2–0.6)	80.0(66.3–89.1)	76.0(66.0–83.8)
EGSYS + NT-proBNP	75.68(58.8–88.2)	83.33(68.6–93.0)	4.54(2.3–9.1)	0.29(0.2–0.5)	80.0(66.5–89.0)	79.5(68.4–87.5)
cTnI + NT-proBNP	72.97(55.9–86.2)	73.81(58.0–86.1)	2.79(1.6–4.8)	0.37(0.2–0.6)	71.1(58.8–80.9)	75.6(63.9–84.4)
EGSYS + cTnI + NT-proBNP	83.78(68.0–93.8)	76.19(60.5–87.9)	3.52(2.0–6.2)	0.21(0.1–0.5)	75.6(63.9–84.4)	84.2(71.6–91.9)

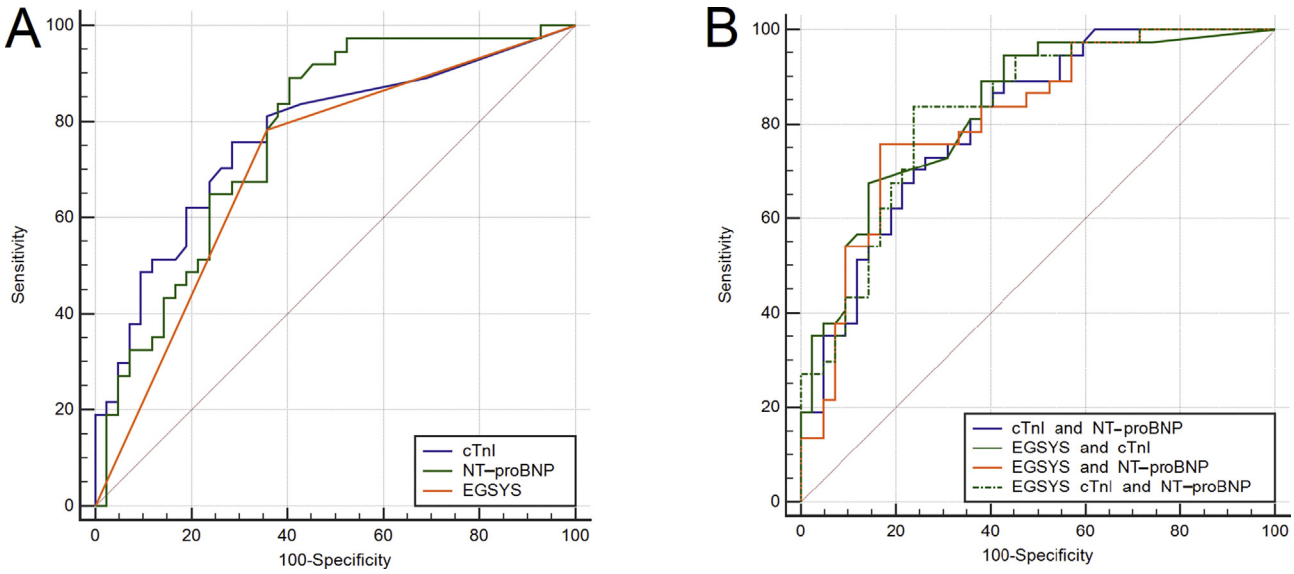

Fig. 2. The ROC curve for the identification of patients with cardiac syncope. (A) The ROC curve for cTnI, NT-proBNP or EGSYS score. (B) The ROC curve for cTnI, NT-proBNP levels and the EGSYS score combined.

Table 3
Comparison of AUCs.

First AUC	Second AUC	P value
EGSYS Score, 0.71(0.60–0.80)	cTnI, 0.77(0.67–0.86)	0.45
EGSYS Score, 0.71(0.60–0.80)	NT-proBNP, 0.77(0.66–0.86)	0.42
EGSYS Score, 0.71(0.60–0.80)	EGSYS + cTnI, 0.83(0.74–0.90)	<0.001
EGSYS Score, 0.71(0.60–0.80)	EGSYS + NT-proBNP, 0.81(0.71–0.89)	0.005
EGSYS Score, 0.71(0.60–0.80)	cTnI + NT-proBNP, 0.81(0.70–0.89)	0.18
EGSYS Score, 0.71(0.60–0.80)	EGSYS + cTnI + NT-proBNP, 0.83(0.73–0.90)	0.007
cTnI, 0.77(0.67–0.86)	NT-proBNP, 0.77(0.66–0.86)	0.96
cTnI, 0.77(0.67–0.86)	EGSYS + cTnI, 0.83(0.74–0.90)	0.21
cTnI, 0.77(0.67–0.86)	EGSYS + NT-proBNP, 0.81(0.71–0.89)	0.53
cTnI, 0.77(0.67–0.86)	cTnI + NT-proBNP, 0.81(0.70–0.89)	0.24
cTnI, 0.77(0.67–0.86)	EGSYS + cTnI + NT-proBNP, 0.83(0.73–0.90)	0.23
NT-proBNP, 0.77(0.66–0.86)	EGSYS + cTnI, 0.83(0.74–0.90)	0.36
NT-proBNP, 0.77(0.66–0.86)	EGSYS + NT-proBNP, 0.81(0.71–0.89)	0.40
NT-proBNP, 0.77(0.66–0.86)	cTnI + NT-proBNP, 0.81(0.70–0.89)	0.34
NT-proBNP, 0.77(0.66–0.86)	EGSYS + cTnI + NT-proBNP, 0.83(0.73–0.90)	0.28
EGSYS + cTnI, 0.83(0.74–0.90)	EGSYS + NT-proBNP, 0.81(0.71–0.89)	0.61
EGSYS + cTnI, 0.83(0.74–0.90)	cTnI + NT-proBNP, 0.81(0.70–0.89)	0.64
EGSYS + cTnI, 0.83(0.74–0.90)	EGSYS + cTnI + NT-proBNP, 0.83(0.73–0.90)	0.93
EGSYS + NT-proBNP, 0.81(0.71–0.89)	cTnI + NT-proBNP, 0.81(0.70–0.89)	0.95
EGSYS + NT-proBNP, 0.81(0.71–0.89)	EGSYS + cTnI + NT-proBNP, 0.83(0.73–0.90)	0.59
cTnI + NT-proBNP, 0.81(0.70–0.89)	EGSYS + cTnI + NT-proBNP, 0.83(0.73–0.90)	0.58

were significantly higher in cardiac syncope. The pathophysiological link between them was not clarified. About one-third of patients in cardiac syncope group was presented acute myocardial infarction, which may due to the included patients were mostly from cardiology department. We supposed the syncope may relate to hemodynamic severity in this setting, and acute myocardial infarction may explain the elevated cTnI and NT-proBNP levels partly.

Unexplained syncope is defined as syncope for which a cause is undetermined after an initial evaluation that is deemed appropriate by the experienced healthcare provider (Shen et al., 2017). A systematic review evaluated implantable loop recorders (ILRs) in unexplained syncope. The results suggested that around 50% of patients finally diagnosed with arrhythmic syncope (Solbiati et al., 2017). Therefore, patients with syncope of undetermined etiology were excluded in AUC analysis.

EGSYS was the only syncope-specific diagnostic score for ED patients reported by A Del Rosso et al., in 2008 (Del Rosso et al., 2008). The diagnostic accuracy of EGSYS was validated in several studies and it was first used to assess hospitalized patients. In our study, comparisons of the AUCs revealed that the EGSYS and biomarkers provided similar diagnosis accuracy. However, the diagnosis accuracy increased when the EGSYS was combined with biomarkers, especially with cTnI.

5. Limitations

There are several limitations of this study that need to be considered. Firstly, this is a single-center, observational study and the sample size was small, and multivariate adjustment was not performed. Secondly, there may be a bias in selecting patients because they mostly hospitalized to the cardiology department, with only few patients admitted to the neurology or other departments. Thirdly, the time from syncope to biomarkers measurement was not available. Thus, the reliability of

conclusions drawn from this analysis may be limited, and future evaluations should include precise timing of biomarker measurements (Christ et al., 2015).

6. Conclusions

The cTnI and NT-proBNP levels were significantly higher in patients adjudicated to have cardiac syncope and the incorporation of both biomarkers to the EGSYS score significantly increased its diagnostic value for cardiac syncope.

CRediT authorship contribution statement

Yan Liang: Conceptualization, Data analysis, Writing- Original draft preparation. **Xiulian Li:** Data analysis, Investigation. **Gary Tse:** Supervision, Writing- Reviewing and Editing. **Wenling Liu:** Investigation, Validation. **Tong Liu:** Project administration, Writing- Reviewing and Editing.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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