Letter to the Editor

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Copeptin as a diagnostic and prognostic biomarker in patients admitted to Emergency Department with syncope, presyncope and vertiginous syndrome

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To the Editor,

Syncope is a transient loss of consciousness (T-LOC) due to global cerebral hypoperfusion characterised by rapid onset, short duration and spontaneous complete recovery. It may be preceded by prodromal symptoms (lightheadedness, nausea, sweating, weakness and visual disturbances). Some patients report signs and symptoms similar to the prodrome of syncope, but without an LOC, a condition called presyncope. However, it is not clear whether the pathophysiological mechanisms involved are the same as in syncope [1]. In other patients, similar symptoms are due to a vertiginous syndrome. Finally, it is often not clear whether an LOC actually occurred.

Currently, no biomarker is included in the guidelines for the diagnosis and management of syncope [1]. Copeptin, a 39-amino acid glycopeptide of unknown function, is the C-terminal portion of provasopressin and is released in an equimolar ratio to vasopressin. Unlike vasopressin, copeptin is very stable in plasma and can be measured with an automated sandwich immunoassay without complex preanalytical requirements [2]. Copeptin may be a suitable biomarker for syncope for two reasons: first, the global cerebral hypoperfusion that causes LOC in syncope is due to arterial hypotension – a stimulus that induces vasopressin secretion; second, syncope constitutes a stress condition, and vasopressin is a stress hormone. Copeptin levels were indeed claimed to correlate with the global stress level of an individual and to be associated to an unfavourable prognosis in several acute conditions [3, 4].

The aim of this study was to evaluate the usefulness of copeptin in a cohort of patients admitted to the Emergency Department (ED) with a T-LOC or its alleged prodromal symptoms: (a) as a diagnostic biomarker, to distinguish syncope from presyncope or vertiginous syndrome; (b) as a prognostic biomarker, to recognize patients at higher risk of short-term rehospitalisation.

The study included 54 subjects admitted to the ED of the University-Hospital of Padua (Italy) reporting a T-LOC or symptoms of a likely imminent T-LOC (blurred vision, dizziness, feeling of faintness) from October to December 2014. Only subjects whose symptoms were of obvious non-syncopal origin (e.g. presentation and medical history strongly suggesting epilepsy) were excluded. Blood samples were obtained soon after admission to ED; after performing the routine blood tests, an aliquot of K_2-EDTA plasma was stored at −80 °C. Copeptin was determined in these samples after thawing and centrifuging 5 min at 3500*g*. The measurement was performed using the *BRAHMS Copeptin-us* assay on the platform Kryptor Compact Plus (ThermoFisher Scientific, Milan, Italy).

The diagnosis of syncope or other conditions was made by clinical criteria. Patients were followed for 45 days after the first ED admission: during this period, all-cause rehospitalisations were registered, excluding only those due to accidents. Data collection was carried out by consulting the patients' clinical records. The study was conducted in accordance with the Declaration of Helsinki and with the hospital's ethical guidelines.

Quantitative variables were expressed as median and range, and qualitative variables as count and percentage. Two-group comparisons were performed by

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Table 1: Demographic and clinical characteristics of the enrolled patients.

Sex, M/F	32/22
Age, years old, median (range)	72.5 (15–95)
Diagnosis of syncope, n (%)	28 (51.9)
Other diagnoses, n (%)	26 (48.1)
Rehospitalisation within 45 days, n (%)	13 (24.1)
Underlying clinical conditions	
Hypertension, n (%)	27 (50.0)
Ischemic cardiopathy, n (%)	13 (24.1)
Neoplasia, n (%)	6 (11.1)
Diabetes, n (%)	3 (5.6)
Trauma, n (%)	7 (13.0)
Other heart disease, n (%)	18 (33.3)
Cerebral ischemia, n (%)	5 (9.3)
Kidney disease, n (%)	6 (11.1)
Vasculopathy, n (%)	7 (13.0)
Infection, n (%)	4 (7.4)
History of syncope, n (%)	8 (14.8)

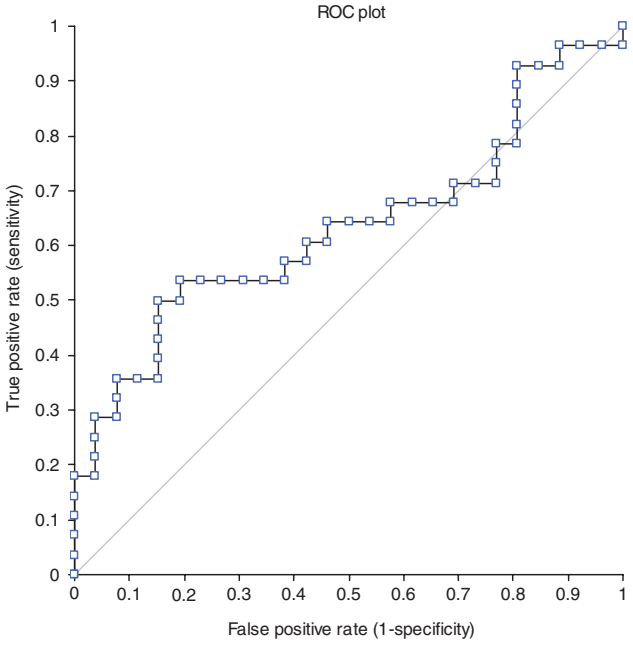

Figure 1: ROC curve for copeptin as a biomarker for diagnosis of syncope.

Mann-Whitney U test, for correlation analyses Spearman rank correlation was used. Receiver-operator characteristic (ROC) curves were constructed to test the accuracy of copeptin as a biomarker and the area under the curve (AUC) was determined. Youden index (true positive rate – false positive rate) was calculated to find the best cutoff. All tests were two-tailed and p-values less than 0.05 were considered to indicate statistical significance. Statistical analyses were performed using Analyse-it for MS Excel (Analyse-it Software Ltd, Leeds, UK).

Demographic and clinical characteristics of the enrolled patients are shown in Table 1. Twenty-eight patients were diagnosed with syncope, 26 with other conditions (presyncope or vertiginous syndrome). Thirteen patients out of 54 were rehospitalised within 45 days of first admission.

The median copeptin plasma concentration was 35.8 pmol/L (range 1.8–1022.0). There was no significant difference between males and females ($p=0.3981$). Plasma copeptin showed a moderate but significant correlation with age (Spearman's $\rho=0.461$, $p=0.0005$). Patients with syncope had a median plasma copeptin concentration of 116.1 pmol/L (range 1.8–1022.0), greater than patients with other conditions (median 20.5 pmol/L, range 2.4–315.0), but the difference was not significant ($p=0.0931$). Patients rehospitalised within 45 days of first admission had a median plasma copeptin of 37.0 pmol/L (range 1.8–1022.0), which showed no significant difference ($p=0.6932$) compared to patients not rehospitalised (median 34.7 pmol/L, range 2.4–678.2).

The ROC curve of plasma copeptin for diagnosis of syncope is shown in Figure 1. The AUC was 0.63, slightly but significantly greater than 0.5 ($p=0.0435$). The ROC-derived best cutoff was 118.2 pmol/L. Using this cutoff to differentiate syncope from other conditions, we obtained a sensitivity of 50.0% (95% CI 30.6–69.4), a specificity of 84.6% (95% CI 65.1–95.6), a positive predictive value of 77.8% (95% CI 48.7–94.5) and a negative predictive value of 61.1% (95% CI 46.5–74.3%).

The ROC curve of plasma copeptin as a prognostic biomarker to predict rehospitalisation within 45 days had an AUC not significantly greater than 0.5 ($p=0.6532$).

Three studies had so far evaluated copeptin in patients with syncope, reporting contrasting results. Lagi et al. [5] compared copeptin plasma levels in 51 subjects with syncope and 51 with accidental falls with minor trauma but without syncope, concluding that copeptin was a reliable test to distinguish these two conditions. Rash et al. [6] compared copeptin plasma levels in 21 vasovagal syncope (VVS) patients, 19 epilepsy patients and 22 healthy controls, finding no significant difference among the three groups. They also found no correlation between copeptin levels and syncope frequency in the prior year. Flevari et al. [7] assessed copeptin plasma levels in 54 patients with history of VVS and 18 healthy controls, before and after tilt test, finding higher levels in patients than in controls only after tilt test. Thus, our study was the first one comparing copeptin levels in subjects with syncope and with "syncope-like" conditions (such as presyncope or vertiginous syndrome). Furthermore, we considered an unselected population, representative of

"real world" patients who are admitted to ED. Finally, our study was the first one evaluating copeptin as a prognostic biomarker for all-cause rehospitalisation in patients with syncope, presyncope and vertiginous syndrome.

Our study had limitations, too. First, the sample size was low. Then, the enrolled patients were non-consecutive because a K_2-EDTA blood sample was not available for everyone; thus, some eligible subjects were probably missed.

According to our data, copeptin does not appear a useful biomarker to distinguish syncope from presyncope or vertiginous syndrome. The distribution of its plasma levels in the two groups was not significantly different, and the AUC of 0.63 did not indicate a good diagnostic performance. Even if we used the ROC-derived best cutoff, we would have missed 14 out of 28 syncope patients, who had plasma copeptin below the threshold.

Copeptin plasma levels were not related to rehospitalisation. Thus, this biomarker proved not useful in identifying patients at major risk of representing themselves to ED and therefore deserving greater attention by clinicians.

In conclusion, our data suggest that copeptin is of limited clinical value both in management and in prognosis of this category of patients.

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