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Comparison between standard and ultrasound-integrated approach for risk stratification of syncope in the emergency department

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Abstract

This prospective cohort enrolled all patients above 16 years of age presenting to the in the emergency department (ED) for a reported syncope was designed to test the accuracy of a point-of-care ultrasound (POCUS) integrated approach in risk stratification. The emergency physician responsible for the patient care was asked to classify the syncope risk after the initial clinical assessment and after performing POCUS evaluation. All risk group definitions were based on the 2018 European Society of Cardiology guidelines. Thirty days after the index event, all participants were followed up to assess the frequency of short-term serious outcomes as defined in the San Francisco Syncope Rule (SFSR) cohorts. We estimated the accuracy of clinical and POCUS-integrated evaluation in predicting SFSR outcomes. Between February 2016 and January 2018, 196 patients were enrolled [109 women (55.6%)]. Median age was 64 years (interquartile range 31 years). After a follow-up of 30 days, 19 patients experienced 20 SFSR outcomes. Positive and negative likelihood ratios were 1.73 (95% CI 0.87–3.44) and 0.84 (95% CI 0.62–1.12) for the clinical evaluation, and 5.93 (95% CI 2.83–12.5) and 0.63 (95% CI 0.45–0.9) for the POCUS-integrated evaluation. The POCUS-integrated approach would reduce the diagnostic error of the clinical evaluation by 4.5 cases/100 patients. This cohort study suggested that the integration of the clinical assessment with POCUS results in patients presenting to the ED for non-high-risk syncope may increase the accuracy of predicting the risk of SFSR outcomes and the usefulness of the clinical assessment alone.

INTRODUCTION

Syncope is defined as a transient loss of consciousness due to cerebral hypoperfusion characterized by short duration, and spontaneous complete recovery [1]. The European Society of Cardiology (ESC) published the first guidelines on this topic almost twenty years ago, and they have been periodically updated [2] since then.

In 2016, a consensus statement on the management of syncope in the Emergency Department (ED) suggested the stratification of patients in three groups: low-, high-, and the new "neither high nor low" (NHNL) risk. This classification was then included in the most recent guidelines [1, 3].

Based on this categorization, ESC guidelines suggest to discharge low-risk patients directly from the ED, and to admit those in the high-risk group. For the patients in the NHNL risk group, who include those at low risk but with comorbidities or with some worrisome features [3], they suggest to observe them for better definition of the cause of the syncope [3].

The risk of patients with syncope varies according to the etiological conditions underlying it, which are, in some cases, difficult to identify. Almost a third of patients with syncope evaluated in the ED is discharged without an etiological diagnosis [4].

At the same time, diagnostic uncertainty often leads many patients classified in the NHNL risk group to a possibly unnecessary hospital admission [1]. These data have been confirmed in several studies, despite a low incidence of adverse events [5]. Therefore, the diagnostic approach to syncope currently used in the ED is expensive and not very effective [6].

In a similar situation, a standardized risk classification, as suggested by current guidelines, is fundamental to guide patients' management.

In the last decade, a "visual" approach to diagnosis using point-of-care ultrasound (POCUS) has been proposed in different settings, including emergency and critical care medicine, with a pretty high accuracy in several pathological conditions (e.g. acutely decompensated heart failure, trauma, shock) [7, 8].

We hypothesize that, during the evaluation in the ED, the integration of POCUS with clinical assessment and electrocardiographic (EKG) results might lead to a better definition of the short-term risk category for patients presenting for syncope, evaluated through the assessment of the occurrence of short-term serious outcomes (i.e., in the first 30 days after ED evaluation). The aim of the present study is to test the accuracy of this POCUS-integrated approach in risk stratification of patients with syncope in the ED.

MATERIALS AND METHODS

This is a single center observational prospective cohort study held at the "Città della Salute e della Scienza di Torino" hospital, Turin, Italy, a tertiary academic center in the Northwestern of Italy.

The institutional review board of the hospital approved the protocol (approval number CS/783) and all patients provided written informed consent to participation.

The study was conducted in accordance with the principles of the Declaration of Helsinki for clinical research involving human subjects.

All patients older than 16 years presenting in the ED for a reported syncope (the index event) were considered eligible. We excluded patients for whom the etiology of the event was identified after the initial clinical assessment (i.e. history, physical exam, and EKG), those who were classified as high-risk patients for short-term serious

outcomes [3], and those who refused to participate in the study (Figure 1).

After the initial clinical assessment, based on the description of the index event, past medical history, physical examination, and EKG, the emergency physician responsible for the patient care was asked to classify the syncope risk [1] (i.e. "clinical gestalt").

All risk group definitions were based on recommendations in the 2016 ESC consensus on management of syncope in the ED, then included in the 2018 ESC guidelines update [1, 3].

Immediately after the clinical evaluation, the same physician performed POCUS, and a new risk assessment, based on the results of both clinical and sonographic findings, was recorded (“POCUS-integrated” definition).

Basic POCUS examination included the evaluation of i) lungs, for the presence of focal or diffuse B-lines (based on an eight-zone scanning protocol [7]), pleural effusion, and sliding; ii) femoral and popliteal veins for ruling out deep venous thrombosis; iii) inferior vena cava for examining the volume status; and iv) heart, for a visual assessment of the ejection fraction (dichotomized as normal or reduced), pericardial effusion (dichotomized as absent or present), and of dilatation of right chambers.

Further, if time and the ability of the providers allowed it, an advanced ultrasound evaluation was performed, including information on mitral annular plane systolic excursion (MAPSE, dichotomized as < or >= 8 mm), regional a- or dys-kinesia of left ventricle, tricuspid annular plane systolic excursion (TAPSE, dichotomized as < or >= 16 mm), dimension of the aortic root, pulmonary artery systolic pressure (< o >= 36 mmHg), and presence of a new severe aortic valve stenosis.

Emergency physicians participating in the present study received a POCUS training based on at least 14 hours of theoretical training followed by 120 bedside supervised evaluations including lung, vascular, inferior vena cava, cardiac ultrasound examinations, as defined by the Italian Society of Emergency Medicine POCUS curriculum [9].

All POCUS evaluations were performed using an intermediate-size ultrasound device equipped with three probes, linear, convex and phased array (Esaote MyLab5 and MyLab7).

The time needed to integrate clinical gestalt and POCUS results was also collected.

Thirty days after the syncope leading to ED presentation, all participants were telephonically followed up by the investigators in order to assess the frequency of short-term serious outcomes as defined in the San Francisco Syncope Rule (SFSR) cohorts, used as a reference in evaluating clinical and POCUS-integrated evaluation accuracy [10, 11].

Patients were not involved in the design, or conduct, or reporting, or dissemination plans of the study at the time this manuscript was submitted.

Descriptive results are presented as numbers and percentages for categorical variables and mean (± standard deviation, SD) or median (and interquartile range, IQR) for continuous variables. The distributions of continuous variables are compared between low and NHNL groups using the Wilcoxon-Mann-Whitney test.

We estimated the accuracy of clinical- and POCUS-integrated evaluation in predicting SFSR outcomes in the first 30 days after presentation to the ED in terms of sensitivity (SE), specificity (SPE), positive predictive value (PPV), negative predictive value (NPV), likelihood ratios (LR), and area under the receiver operating

characteristic (ROC) curve [12]. Accuracy of both evaluations was compared using the McNemar test for paired data [13].

In addition, the clinical usefulness of the POCUS-integrated approach was also evaluated by the category-based net reclassification index (NRI) [14], and the use of reclassification tables, net benefit (NB), and decision curve analysis (DCA) [15].

NRI quantifies how many times a risk-category changes by virtue of a new test result.

NB quantifies the possible diagnostic gain as the benefit (of a true positive compared to a false negative) minus the harm (of a false positive compared to a true negative) for a given threshold probability of high-risk syncope.[14, 15]

Assuming a SPE of approximately 92% of the POCUS-integrated evaluation, a 85% power and a 5% alpha error, we estimated that a sample size of 192 patients would be sufficient to test a 15% SPE difference between clinical only and POCUS-integrated evaluation.

Statistical analyses were conducted using STATA software, version 13.1 (Stata Corporation, College Station, Texas, USA).

RESULTS

From February 2016 and January 2018, 424 patients presenting with a possible syncope to the ED were evaluated for eligibility. Of these, 201, all of them in the low- and NHNL risk classes, were enrolled for the POCUS evaluation by 18 emergency physicians, about 70% of the total number of staff physicians (median evaluations per physician 9.5, iqr 5 - Figure 1). Median age was 64 years (interquartile range, IQR, 30

years); 110 women (54.7%) and 91 men (45.3%) were enrolled (Figure 1).

Baseline characteristics of patients and ED outcomes are detailed in Table 1.

After a 30-days follow-up, 22 patients experienced 30 SFSR-defined outcomes (Table 1). Three patients died during the 30 days follow up, two women (aged 89 and 88 years, respectively) and a man (52 years old). The male patient was admitted for tamponade and, during his hospital stay, an advanced, pluri-metastatic lung cancer was diagnosed. The older female patient was admitted for multifocal bilateral pneumonia. The second female patient was admitted for hyponatremia and hypokalemia but experienced stroke and myocardial ischemia during hospital stay, seven days after the ED evaluation.

Table 2 reports the frequency of basic and advanced POCUS evaluations performed and their results.

The SE of the clinical and the POCUS-integrated evaluations was 31.8% (95% confidence interval, CI, 13.9-54.9%) and 40.9% (95% CI 20.7-63.6%), respectively ($p=0.05$), and the SPE was 81% (95% CI 74.5-86.5%) and 92.7% (95% CI 87.9-96.1%), respectively ($p<0.01$). Positive and negative predictive values were 17.1% (95% CI 7.2-32.1%) and 90.6% (95% CI 85-94.7%) for the clinical evaluation, and 40.9% (95% CI 20.7-63.6%) and 92.7% (95% CI 87.9-96.1%) for the POCUS-integrated evaluation, respectively. Positive and negative likelihood ratios were 1.68 (95% CI 0.85-3.31) and 0.84 (95% CI 0.63-1.13) for the clinical evaluation, and 5.63 (95% CI 2.73-11.6) and 0.64 (95% CI 0.45-0.9) for the POCUS-integrated evaluation.

Figure 2 shows the ROC curves for the two diagnostic approaches.

NRI for outcomes and non-outcomes during the follow up was 9.1% and 11.7%, respectively (Table 3).

Figure 3 shows the decision curves for clinical and POCUS-integrated approaches along with two additional possibilities, one of them considering all syncopes as at high-risk of experiencing SFSR event during the follow up period (i.e., the "treat all" curve), and a second curve considering all episodes as low-risk syncopes (i.e. the "treat none" curve). The distance between clinical and POCUS-integrated curves represents the net advantage of POCUS-integrated evaluations in terms of net benefit at each probability of high-risk syncope (the intersection between clinical evaluation and treat none curve is the cohort prevalence of SFSR events).

Using the prevalence of SFSR outcomes in our cohort (10.9%) as a threshold probability, the use of the POCUS-integrated approach would reduce the diagnostic error of the clinical evaluation by 4.5 cases/100 patients (decision curves are shown in Figure 3).

The median time between clinical and POCUS-integrated approach, measured from the starting time of the clinical evaluation to POCUS performance was 15 minutes (iqr 20 minutes), and median time for performing basic POCUS evaluations was 7 minutes (iqr 3.5 minutes).

DISCUSSION

This mono-centric cohort study suggests that the integration of the clinical gestalt with POCUS results in patients presenting to the ED for non high-risk syncope may increase the accuracy in predicting the risk of SFSR outcomes and the usefulness of the clinical assessment alone.

Syncope is a quite rare symptom at presentation in the ED, accounting for about 1% of all visits in the United States of America between 2001 and 2010 [16].

Even after performing the diagnostic tests recommended by the ESC guidelines, a high percentage (20-40%) of events is still classified as of "unknown origin" [3]. Some newly proposed biomarkers (e.g. MMP-7, and TIM-1 [17]) and biomarkers indicated for different diseases (e.g. Nt-proBNP and troponin [18]) have been evaluated in order to decrease this uncertainty but none of them seemed capable to increase the clinically-based accuracy in the ED significantly and, consequently, none was accepted for routine practice [1, 5].

The use of POCUS has been increasing exponentially from the beginning of this century in most medical settings, not only in the ED. In general, POCUS should not be considered as an imaging test but as an integration to the clinical examination [8].

For some cardiac diseases, POCUS was shown to be more accurate than the usual approach, based on physical examination, EKG, and laboratory tests, and, in some instances, it has been proposed to be included in the initial evaluation in the ED (e.g. for dyspneic patients with suspicion of decompensated heart failure) [19, 20].

In our cohort, the clinical gestalt showed a modest accuracy for correctly identifying high-risk syncopes, similar to that reported in the international literature [1, 5]. Indeed, by definition, syncope has often a transient cause, difficult to identify during the examination [1].

By adding the POCUS results to the clinical examination, the accuracy of the integrated approach increased of about 10%. In particular, our results suggested that the integrated approach has a high SPE, allowing a good discrimination of NHNL cases that are at risk of serious event in the short term, significantly higher than that of the clinical approach alone. Although also the SE of the POCUS-integrated approach was significantly higher than that of the clinical evaluation alone, we consider this gain not

sufficiently high to exclude a possible short-term serious outcome, and therefore less clinically relevant. The integration with POCUS increases both SPE and SE with a different clinical impact. The difference in SE does not seem sufficient to exclude a high-risk syncope in the ED. This is likely related to the large number of possible etiologies of high-risk syncopes, only a part of which could be identified during ED or hospital stay, mostly by exclusion [1, 4]. On the other side, the POCUS-integrated increased SPE significantly improves the ability to detect the likelihood of a high-risk syncope.

Bedside ultrasound is a relatively cheap diagnostic tool, easy to repeat and with reproducible results, and it can be performed by operators with a limited training [7], at least for all the basic examinations evaluated in the present study [21].

Our results also added evidence to the clinical usefulness of the POCUS-integrated approach using NRI, NB, and DCA (Table 3 and Figure 3).

Clinical usefulness was defined as the extension of improvement in health outcomes (e.g., reduced number of SFSR outcomes) compared to the current best alternative by a diagnostic test [13]. In our study, clinical usefulness is represented by the possibility to correctly identify patients with a high risk of short-term adverse events initially classified as low or NHNL risk.

The stratification based on the clinical gestalt slightly improved that obtained using an approach that theoretically consider all syncopes as high risk (figure 3, "treat all" vs "clinical evaluation" curves). The POCUS-integrated approach reduced errors in risk categorization in 4.5% of cases compared to the clinical-approach (figure 3, "POCUS-integrated evaluation" curve). Current guidelines suggest to discharge or to observe the non high-risk syncope patients, and to admit the others considering the risk of short-

term malignant outcomes, and in order to better define their etiology. In this scenario, a POCUS integrated approach seems to have the ability to reduce errors in categorizing syncopes regardless of their etiology.

As mentioned above, however, some syncopes could also have an electrical etiology that cannot be detected by POCUS but might be hypothesized on the basis of event history and EKG. For this reason, the usefulness of an integration of POCUS with the clinical evaluation for syncope could be higher in a cohort of patients with a clinically "not-electrical" syncope.

Our study also estimated the time between the clinical and the integrated evaluation, which was relatively short in an ED setting. This also reasonably excludes that any relevant change in POCUS results might have occurred due to treatments that have started in the meanwhile.

The study has some strengths and limitations.

To our knowledge, this is the first paper evaluating the accuracy and clinical usefulness of a POCUS-integrated approach among non high-risk syncope patients in the ED.

Several scores have been proposed for the long-term risk assessment after syncope (i.e. OESIL, EGSYS, MK, and SFSR [10, 11, 22–24]). However, a recent study suggested that most of these scores overestimate this risk [25] and, equally important, seem unable to avoid hospitalization of a large proportion of patients after the ED evaluation (12-86% [5]). Our results, which focused on short-term risk assessment, may help in distinguishing, among non high-risk patients, those needing admission from those who can be safely addressed to other follow-ups, after discharge.

The skills requested for the POCUS evaluation were basic and did not require an additional specific training of the participant physicians as they are part of the training curriculum not only in Italy [9] but also in Europe and in USA [26, 27].

Our study collected data also on the advanced POCUS examinations. These data were available only for some enrolled patients (from 26.4% for systolic pulmonary arterial pressure to 65.7% for aortic root) and further specific studies will be needed for clarifying the possible role of these more advanced POCUS examinations.

Another advantage is the small time needed to perform POCUS in our setting. In our institution, three ultrasound machines were simultaneously available for patients' evaluation in the ED (i.e., one for each examination room). These results should be confirmed in different-resources hospitals. A longer time could affect the integrated approach performance based on the treatment ordered and administered in the meanwhile.

The enrolment process needed the presence of a physician able to perform all the POCUS evaluations. This condition has not been fulfilled in all shifts in our ED during the study period or for all physicians on call. Due to this situation, we likely missed some index events. It is unlikely that this has introduced a selection bias in our cohort, because the presence of staff physicians in the ED was independent from their skills in bedside ultrasound, implying that patients would be randomly missed in every shift.

CONCLUSION

In conclusion, the integration of POCUS with the clinical evaluation of non high-risk syncopes in the ED may increase the specificity in classifying correctly short-term risk patients and be helpful in identifying the patients who need to be hospitalized for tighter

monitoring and/or further diagnostic work-up. However, the modestly increased sensitivity does not seem enough high to allow physicians to exclude high risk syncope in the ED. The implantation of POCUS approach to syncope in the ED needs to be planned and further evaluated after its use will be largely adopted.

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Figure legends.

Figure 1. Flow chart of participants in the study. (TLOC: transient loss of consciousness; ED: emergency department; MI: myocardial infarction; HF: heart failure; EF: ejection fraction; EKG: electrocardiogram; cQT: corrected QT interval; VT: ventricular tachycardia; Hb: hemoglobin; K^+: potassium plasmatic concentration; POCUS: point-of-care ultrasound; NHNL: neither high nor low risk syncope; SFSR: San Francisco Syncope rule score)

Figure 2. Area under the ROC curve for the clinical and the POCUS-integrated evaluations (p 0.07 - ROC: receiver operating characteristic curve; POCUS: point-of-care ultrasound)

Figure 3. Decision curves for the clinical and the POCUS-integrated evaluations. (POCUS: point-of-care ultrasound). The distance between clinical and POCUS-integrated curves represents the net advantage of POCUS-integrated evaluations in terms of net benefit at each probability of high-risk syncope.

Tables.

Table 1. Baseline characteristics of enrolled patients and list of San Francisco Syncope Rule (SFSR) events during the 30-days follow up period, by level of syncope risk at presentation to the ED

	low risk syncopes	neither low nor high risk syncopes
median age (IQR)	61.5 years (31.5)	69 (22)
male/female ratio	0.78	1.05
active smoking habit % (n)	21.4% (28)	21.2% (7)
arterial hypertension % (n)	34.4% (55)	56.1 (23)
diabetes % (n)	10% (16)	9.8% (4)
dislypidemia % (n)	15 % (24)	24.4% (10)
respiratory failure % (n)	1.9% (3)	-
liver failure % (n)	-	4.9% (2)
cerebrovascular disease % (n)	6.3% (10)	14.6% (6)
active cancer % (n)	9.4% (15)	19.5% (8)
chronic renal failure % (n)	1.3 % (2)	7.3% (3)
Vital at the presentation to the ED - median (IQR)		
Clinostatic systolic pressure (mmHg)	126 (30)	120 (35)
Clinostatic diastolic pressure (mmHg)	80 (10)	70 (10)
Temperature (°C)	36°C (0.8)	36°C (0.5)
Pulse rate (bpm)	75.5 (14)	75 (25)
O2 saturation (%)	98% (2)	97% (2)
Admission % (n)	13.8 (22)	19.5 (8)
Discharge % (n)	53.1 (85)	29.3 (12)
Admission after observation % (n)	2.5 (4)	4.9 (2)
Discharge after observation % (n)	30.6 (49)	46.3 (19)
SFSR outcomes		
death, events (%)	2 (1.26%)	1 (2.4%)
acute myocardial infarction, events (%)	none	none
arrhythmia, events (%)	2 (1.3%)	2 (4.9%)
pulmonary embolism, events (%)	1 (0.6%)	none
stroke, events (%)	1 (0.6%)	none
subarachnoid hemorrhage, events (%)	none	none
significant hemorrhage, events (%)	3 (1.9%)	none
any condition causing a return visit to the ED, events (%)	7 (4.4%)	4 (9.8%)

re-admission to hospital, events (%)	2 (1.3%)	1 (2.4%)
aortic dissection, events (%)	none	none
any acute intervention/precedure, events (%)	4 (2.5%)	none
Total, events (%)	22 (13.2%)	8 (19%)

Table 2. Frequency of basic and advanced point-of-care ultrasound evaluations performed and their results (* evaluation of aortic valve was defined as doppler assessment of severe aortic stenosis)

	normal - n (%)	pathological - n (%)	not evaluated - n (%)
Basic evaluations			
focal B-lines	194 (96.5%)	7 (3.5%)	-
diffuse B-lines	193 (96%)	8 (4%)	-
pleural sliding	201 (100%)	-	-
pleural effusion right left	 201 (100%) 200 (99.5%)	 - 1 (0.5%)	 - -
femoral and/or popliteal DVT	201 (100%)	-	-
IVC dimension	195 (97%)	6 (3%)	-
IVC collapsability	191 (95%)	10 (5%)	-
visual EF	199 (99%)	2 (1%)	-
cardiac right chambers dilated	199 (99%)	2 (1%)	-
pericardial effusion	198 (98.5%)	3 (1.5%)	-
Advanced evaluations			
MAPSE	78 (38.8%)	7 (3.5%)	116 (57.7%)
TAPSE	88 (43.8%)	6 (3%)	107 (53.2%)
dilated aortic root	129 (64.2%)	3 (1.5%)	69 (34.3%)
left ventricle wall motion	116 (57.7%)	6 (3%)	79 (39.3%)
aortic valve*	96 (47.8%)	5 (2.5%)	100 (49.7%)
systolic pulmonary arterial pressure	52 (25.9%)	1 (0.5%)	148 (73.6%)

Table 3. Reclassification tables for clinical and POCUS-integrated evaluation in

predicting San Francisco Syncope rule (SFSR) outcomes. POCUS: point-of-care ultrasound

Patient with low risk syncope		POCUS-integrated			**Patients with NHNL risk syncope**		POCUS integrated		
		low risk syncope	NHNL risk syncope	*Total*			low risk syncope	NHNL risk syncope	*Total*
Clinical gestalt	low risk syncope	143	2	*145*	Clinical gestalt	low risk syncope	11	4	*15*
	NHNL risk syncope	23	11	*34*		NHNL risk syncope	2	5	*7*
	Total	*166*	*13*	*179*		*Total*	*13*	*9*	*22*