Risk Stratification of Syncope in the Emergency Department

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Syncope is defined as transient loss of conscious (TLOC) due to cerebral hypoperfusion. It is characterized by a rapid onset, short duration, and spontaneous complete recovery. This definition includes reflex syncope, orthostatic hypotension, and cardiac causes. This definition does not include TLOC due to head trauma, epileptic seizures, psychogenic TLOC, or other rare causes [1]. Estimates on the frequency of visits (0.6–1.7%) to emergency department (ED) and subsequent rates of hospitalizations (12–85%) vary according to country [2]. Studies evaluating the short-term (7–30 days) outcomes in syncope patients admitted to the ED estimate that 0.8% die and 10.3% have a non-fatal severe outcome. Of non-fatal severe outcomes (e.g., clinical deterioration, serious injury with recurrence, or a significant therapeutic intervention), 6.9% occur while in the ED and another 3.6% have a post-ED serious outcome. Other studies have shown that both short- and long-term mortality rates among syncope patients discharged from the ED were very low (0.4% at 30 days and 3.0% at 1 year). In comparison, among admitted patients, mortality rates were at least four times higher at 30 days and at least three times higher at 1 year [3].

One of the new concepts in the most updated European Society of Cardiology (ESC) guidelines for the diagnosis and management of syncope [1] is the approach to patients admitted to the ED regarding risk stratification and regarding the disposition from ED. This disposition includes either discharging, hospitalizing, or observing the patients in the ED or in a syncope unit. Initial syncope evaluation in the ED consists of detailed history taking and physical examination, including supine and standing blood pressure measurements and 12-lead electrocardiogram (ECG). Based on these findings, additional examinations may be performed when needed, including immediate ECG monitoring, echocardiogram, carotid sinus massage in patients over the age of 40 years, head-up tilt test, and blood work.

The management of TLOC of suspected syncopal nature in the ED should answer the following three key questions:

- *Is there a serious underlying cause that can be identified?* The primary aim for an ED clinician is to establish an underlying diagnosis, especially those associated with the potential for rapid clinical deterioration
- *What is the risk of a serious outcome?* It is the acute underlying disease that most frequently determines the short-term adverse events rather than the syncope itself [4]
- *Should the patient be admitted to the hospital?*

Risk stratification in the ED is important for two reasons: to recognize patients with a likely low-risk condition who are able to be discharged with adequate patient education and to recognize patients with a likely high-risk cardiovascular condition requiring urgent investigation that may require admission.

High-risk patients are more likely to have cardiac syncope (i.e., structural heart disease or electrical disease), which is a major risk factor for sudden cardiac death and overall mortality [5,6]. Orthostatic hypotension is associated with a two-fold higher risk of death compared with the general population, probably due to co-morbidities [7]. Low-risk patients are more likely to have reflex syncope with an overall excellent prognosis [8].

The guidelines list high-risk features that suggest the presence of serious underlying cause and low-risk features that suggest a benign underlying cause [1].

Some authors believe that the approach of the guidelines could be further improved by defining intermediate-risk criteria for patients who are neither high-risk nor low-risk, thus making the prognostic stratification table easier to remember and use in the crowded ED; by clarifying the role of laboratory tests to support the clinical judgment; and by defining protocols for managing patients in ED observation unit [9]. The role of recurrency of syncope in decision making in the ED is a matter of ongoing investigation as well [10].

Numerous prediction tools exist to help reduce unnecessary hospitalizations and healthcare costs related to syncope care [2,11,12]. The use of clinical decision making rules and standardized protocols has not changed the rate of hospitalizations significantly. None of these rules are used widely in EDs due to inconsistent definitions of syncope, outcomes, outcome time frames and predictors, small sample size, poor sensitivity and specificity reported from external validation, or due to limited external validation [13].

Syncope clinical decision rules were found to perform no better than clinician judgment at predicting short-term serious

outcomes [14], and most syncope deaths and many poor outcomes are associated with underlying illness rather than syncope per se, particularly in the long term [15]. Therefore, the ESC guidelines suggest that clinical decision algorithms should not be used alone to perform risk stratification in the ED [1].

With regard to disposition, although it is crucial to identify the high-risk patients to ensure early, rapid, and intensive investigation, not all patients at high-risk need hospitalization [12]. However, unnecessary admission in low-risk patients can be harmful as well [16]. The implementation of new organizational approaches and care pathways, such as syncope inpatient observation units (located in ED or cardiology or internal medicine departments) and outpatient units, may offer safe and effective alternatives to admission in cases of intermediate-risk patients .Randomized clinical trials that have evaluated ED-based syncope units compared with usual care, demonstrated higher diagnostic yield, lower hospital admission, reduced costs, and no increase in adverse outcomes in patients randomized to the syncope unit [17]. The European Heart Rhythm Association task force developed consensus-based preliminary quality indicators for evaluation of a syncope unit [18].

The targets include the following criteria:

- An absolute rate of undiagnosed TLOC should be reduced by 20%
- < 20% of low-risk/intermediate-risk (unexplained) TLOC patients should be admitted from the ED
- The syncope unit should have a 20% reduction in costs relative to usual practice and should have improved outcomes (< 5% readmissions for syncope and < 20% of paced patients with recurrence at 1 year).

When developing a standardized process for unexplained syncope, templates of metrics to track progress and potential benefits of standardization (before and after standardization) should be created. For example, ED metrics (e.g., number of TLOC visits, mean number of tests performed per case, mean time spent in ED, number of undiagnosed TLOC at disposition, admission rate, readmission rate within a certain period of time); hospital metrics (e.g., number of undiagnosed TLOC admitted, mean number of tests performed per case, mean length of stay, ratio of cases diagnosed at discharge, mean cost per case, mean reimbursement per case, mean patient satisfaction rate); and testing costs and number of tests that helped determine etiology should be included.

The Boston Syncope Criteria (BSC) is a comprehensive pathway designed to effectively identify patients at risk for adverse outcomes that require inpatients admission and workup and designed to identify patients who cannot be discharged. Its advantage lies in its comprehensive 25-point set of diagnostic criteria that mimic the thinking pathway of a clinician in ED regarding risk stratification and disposition of patients with syncope. This rule was validated in 2007 [11], showing a sensitivity of 97% (62% specificity) and a negative predicted value (NPV) of 99% for 30-day adverse outcomes. This rule was implemented in Boston (USA) in a prospective before-and-after cohort study [19]. In the *before* phase 59% of patients were admitted and 5% were placed in an observation ward. Some 3% who were discharged from the ED had critical intervention within 30 days and 10% returned to the ED. After the pathway was implemented, there was a significant reduction in patients admitted (34%, $P < 0.001$) and 20% were placed in an observation unit. Some 3% of discharged patients had critical interventions at 30 days and there was a reduction in percentage of patients who returned (3%, $P = 0.001$).

In this issue of the *Israel Medical Association Journal* (*IMAJ*) [20] Muhtaseb et al. published the results of a retrospective application of the BSC on 200 patients admitted over a one-year period to an urban tertiary care hospital in Jerusalem with syncope. The decision to admit or discharge a patient was based on the clinical decision of the treating doctor and not on the BSC. The authors measured the ability of this rule to identify low-risk patients or to identify patients at risk for clinical interventions/adverse outcomes based on the BSC, knowing the 30-day outcome according to available medical records. The BSC had sensitivity of 95%, specificity of 66%, and an NPV of 99%. The study was limited by its retrospective design, the fact that researcher had access to information from medical records only for 3 months, and the deprivation of a short-stay observation unit. Despite these limitations, the article by Muhtaseb and colleagues [20] includes three important messages about the BSC rule:

- It is applicable even outside the United States, in a different medical environment
- It has a high NPV, which may aid ED physicians in safely discharging low-risk syncope patients
- It does not substitute clinical judgment, as guidelines suggest, but works in an additive way to clinical judgment

CONCLUSIONS

The BSC rule may help organize the pathway of syncope patients in the ED, standardize it, and help in achieving the quality targets and in improving the measurement of progress.

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Capsule

Cell death limits pathogens

During infection, *Yersinia* inhibition of the protein kinase TAK1 triggers cleavage of the pore-forming protein gasdermin D (GSDMD), which leads to a kind of inflammatory cell death called pyroptosis. In a genome-wide screen, **Zheng** et al. identified a lysosome-tethered regulatory supercomplex as being a critical driver of *Yersinia*-induced pyroptosis. The activity of the GTPase Rag and lysosomal tethering of Rag-Ragulator were required to recruit and activate the kinase RIPK1 and protease caspase-8 to cleave GSDMD, which causes cell death and limits infection. By contrast, Rag-Ragulator was not required for inflammasome-mediated pyroptosis. Thus, metabolic signaling on lysosomes can regulate cell death during pathogenic bacterial infection.

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Capsule

A role for IgA in malaria

Immunoglobulin A (IgA) is known to play a protective role against pathogens at mucosal surfaces. However, the protective effects of IgA in the serum are less well understood, particularly in the context of pathogens such as *Plasmodium falciparum*. **Tan** et al. isolated and characterized serum IgA from three independent cohorts of humans exposed to *P. falciparum*. The authors also studied IgA antibodies isolated from individuals who were consistently resistant to malaria and found that these antibodies bound to a conserved site on sporozoites and were protective in mouse models in vivo. These results establish a role for serum IgA in the context of malaria and suggest a region of the circumsporozoite protein as a target for protective antibodies.

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