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International Validation of the Canadian Syncope Risk Score

A Cohort Study

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Background: The Canadian Syncope Risk Score (CSRS) was developed to predict 30-day serious outcomes not evident during emergency department (ED) evaluation.

Objective: To externally validate the CSRS and compare it with another validated score, the Osservatorio Epidemiologico della Sincope nel Lazio (OESIL) score.

Design: Prospective cohort study.

Setting: Large, international, multicenter study recruiting patients in EDs in 8 countries on 3 continents.

Participants: Patients with syncope aged 40 years or older presenting to the ED within 12 hours of syncope.

Measurements: Composite outcome of serious clinical plus procedural events (primary outcome) and the primary composite outcome excluding procedural interventions (secondary outcome).

Results: Among 2283 patients with a mean age of 68 years, the primary composite outcome occurred in 7.2%, and the composite outcome excluding procedural interventions occurred in 3.1% at 30 days. Prognostic performance of the CSRS was good for both 30-day composite outcomes and better compared with the OESIL score (area under the receiver-operating characteristic curve [AUC], 0.85 [95% CI, 0.83 to 0.88] vs. 0.74 [CI, 0.71 to 0.78] and 0.80 [CI, 0.75 to 0.84] vs. 0.69 [CI, 0.64 to 0.75], respectively). Safety of triage, as measured by the frequency of the primary composite outcome in the low-risk group, was higher using the CSRS (19 of 1388 [0.6%]) versus the OESIL score (17 of 1104 [1.5%]). A simplified model including only the clinician classification of syncope (cardiac syncope, vasovagal syncope, or other) variable at ED discharge—a component of the CSRS—achieved similar discrimination as the CSRS (AUC, 0.83 [CI, 0.80 to 0.87] for the primary composite outcome).

Limitation: Unable to disentangle the influence of other CSRS components on clinician classification of syncope at ED discharge.

Conclusion: This international external validation of the CSRS showed good performance in identifying patients at low risk for serious outcomes outside of Canada and superior performance compared with the OESIL score. However, clinician classification of syncope at ED discharge seems to explain much of the performance of the CSRS in this study. The clinical utility of the CSRS remains uncertain.

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† For members of the BASEL IX Investigators, see the **Appendix** (available at Annals.org).

Most causes of syncope are benign, but some, particularly cardiac causes, may be life-threatening (1, 2). Distinguishing patients at low risk for adverse events from patients at high risk during evaluation in the emergency department (ED) is challenging, especially in older patients, because the incidence of cardiac syncope and its associated serious adverse outcomes increases with age (3–5). In 3% to 5% of patients presenting to the ED with syncope, the serious condition that caused syncope will be detected only after ED disposition (1, 2, 6, 7). In the absence of accurate risk stratification, this uncertainty leads to hospitalization in up to 80% of patients, with associated costs exceeding $2.4 billion in the United States annually (1, 2, 7, 8).

Several risk scores have been developed to help in the triage of patients with syncope. Some focus on medical history, clinical variables, and the electrocardiogram (ECG) (9–11), whereas others additionally require laboratory tests (12–14). However, none of the previously developed scores have been widely adopted in clinical practice (1, 2). Reasons for this include modest sample size, suboptimal performance, controversy on what outcomes to predict, and lack of external validation (15–17). The Canadian Syncope Risk Score (CSRS) was developed to predict a composite of serious clinical plus procedural events at 30 days not evident during ED evaluation (7). Although initial national validation showed high prognostic accuracy, 2 small validation studies found only moderate performance (6, 18, 19). By including the final clinician classification of syncope in the ED (cardiac, vasovagal, or other), the CSRS is not meant for early triage purposes but as a decision tool after completed ED assessment. The primary aim is to help in the identification of patients at low risk for 30-day serious outcomes in whom hospitalization, which is associated

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with low diagnostic yield and high costs, can be avoided (1, 2).

Overall, the performance and clinical utility of the CSRS in patients with syncope presenting to the ED in countries outside of Canada is largely unknown. In addition, it is unknown how well the CSRS predicts a composite of only serious clinical outcomes rather than the previously used composite that also included procedural interventions. No comparison of performance has been made between the CSRS and another validated prognostic syncope risk score—for example, the Osservatorio Epidemiologico della Sincope nel Lazio (OESIL) score (10). Furthermore, it is unknown whether the CSRS also allows for the prediction of serious outcomes beyond 30 days. We aimed to address these gaps in knowledge and validate the CSRS in a large, international, multicenter study.

METHODS

Study Design, Setting, and Population

The BASEL IX (BAsel Syncope EvaLuation) study (ClinicalTrials.gov: NCT01548352) is a prospective, international, multicenter study enrolling patients aged 40 years or older presenting to the ED with syncope within the past 12 hours in 14 hospitals across 8 countries (United States, Switzerland, Spain, Germany, Italy, Poland, New Zealand, and Australia). Patients were recruited immediately after ED presentation, thereby ensuring unselected recruitment regardless of the later triage decision regarding admission versus outpatient management.

Patients with a nonsyncopal loss of consciousness (for example, fall, presyncope, stroke, epilepsy, or intoxication) and patients with a missing 12-lead ECG were excluded from the analysis. In line with the original derivation of the CSRS, patients with an adverse event or indication for a procedural intervention that was part of the composite end point, identified during or immediately before the index ED evaluation, were also excluded from the analysis. Furthermore, in patients enrolled more than once, only the first enrollment was used. The BASEL IX study was done according to the principles of the Declaration of Helsinki and approved by regional ethics committees. Written informed consent was obtained from all patients. Reporting is in accordance with TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis) guidelines (20).

Clinical Assessment and Final ED Classification of Syncope

All patients had a thorough and standardized clinical assessment, including a medical history and a history of the circumstances of the current event, physical examination, and measurement of vital parameters. Twelve-lead ECG recordings were obtained according to local standard operating procedures at ED presentation. Opposite to the original derivation study (7), the BASEL IX study protocol did not restrict timing and extent of (cardiac) work-up in the ED, which was left to the discretion of the attending physicians who were advised to operate according to clinical practice guidelines (1, 2). The final ED classification of syncope (clinician classification of syncope) was determined by the treating physician after completed ED evaluation, integrating the information provided by the diagnostics they decided to perform or order and documented in the ED discharge letter (see section 1 of the **Supplement**, available at Annals.org). No specific training was mandatory for ED physicians in participating centers to maximize generalizability of the findings.

CSRS and OESIL

The CSRS combines 9 predictors derived from the clinical evaluation, cardiac troponin (cTn), 12-lead ECG, and clinician classification of syncope (vasovagal, cardiac, or other) after ED evaluation (**Table 1**) (7). The OESIL score, which was derived and validated to predict 1-year mortality and has been used as a prognostic comparator in prior studies (4, 21), is based on 4 predictors: age greater than 65 years, history of cardiovascular disease, syncope without prodrome, and abnormal ECG (**Table 1**) (10).

Follow-up

Patients were contacted by trained physicians or study nurses at set intervals (6, 12, and 24 months) after discharge either in written form or by telephone, where details about serious outcomes during the entire follow-up period were obtained. Four sources of follow-up information were available: patients (or their relatives in case of deceased or incapacitated patients); hospital records, including the index hospitalization; records of physicians in private practice; and local or national death registries. At least 1 of the latter 3 was obtained for verification whenever possible.

Outcome Measures

Primary prognostic outcome measures were 2 composites summarizing 30-day serious outcomes not evident in the ED: first, a composite measure of serious clinical and procedural outcomes (primary composite outcome), similar to the CSRS derivation study, including death, life-threatening arrhythmia, myocardial infarction, serious structural heart disease, aortic dissection, pulmonary embolism, severe pulmonary hypertension, severe hemorrhage, any other serious condition causing syncope, and procedural interventions for the treatment of syncope; second, to address the possibility of a causal chain between hospitalization and procedural intervention (for example, pacemaker implantation) for the treatment of syncope, a purely clinical composite outcome measure including all of the above except procedural interventions (composite outcome excluding procedural interventions). Both composite outcomes did not include any asymptomatic arrhythmia, nor symptomatic supraventricular arrhythmia, because this is a more benign event with often unclear association with the cause of syncope and, on its own, may not justify hospitalization (22). Secondary measures included both composite outcomes within 720 days of follow-up.

Blood Sampling and Laboratory Methods

Venous blood samples were drawn on arrival to the ED and processed and/or frozen at −80 °C for storage

Table 1. Predictors and Associated Points of the CSRS and OESIL Score With the Respective Number and Proportion of Patients per Item in the Cohort (Total *n* = 2283 Patients)*

Category	Points	Patients, *n* (%)
CSRS		
Clinical evaluation		
Predisposition to vasovagal syncope†	−1	531 (23.3)
History of heart disease‡	1	842 (36.9)
Systolic blood pressure reading <90 or >180 mm Hg§	2	128 (5.6)
Investigations		
Elevated troponin level (>99th percentile)	2	280 (12.3)
Abnormal QRS axis (<−30° or >110°)	1	385 (16.9)
QRS duration >130 ms	1	238 (10.4)
Corrected QT interval >480 ms	2	217 (9.5)
Clinician classification of syncope at emergency department discharge		
Vasovagal syncope	−2	899 (39.4)
Cardiac syncope	2	269 (11.8)
Other	0	1115 (48.8)
Total score	(−3 to 11)	–
OESIL		
Clinical evaluation		
Age >65 y	1	1397 (61.2)
History of cardiovascular disease‖	1	764 (33.5)
Syncope without prodrome	1	496 (21.7)
Investigations		
Abnormal electrocardiogram¶	1	1001 (43.8)
Total score	(0 to 4)	–

CSRS = Canadian Syncope Risk Score; OESIL = Osservatorio Epidemiologico della Sincope nel Lazio.
*The CSRS combines 9 weighted predictors, with points ranging from −2 to +2 for each item, resulting in a total score range of −3 to +11 points. The OESIL score consists of 4 predictors, each worth 1 point, resulting in a score range of 0 to +4 points. Reference category for the syncope classification item of the CSRS is "other" (including unknown) (for more details, see section 1 of the Supplement, available at Annals.org). For both scores, all other predictors are binary (yes/no), with the reference category being "no."
† Triggered by being in a warm, crowded place; prolonged standing; fear; emotion; or pain.
‡ Includes coronary or valvular heart disease, cardiomyopathy, congestive heart failure, and non–sinus rhythm (electrocardiogram evidence during index visit or documented history of ventricular or atrial arrhythmias, or device implantation).
§ Includes any of the blood pressure values during emergency department evaluation.
‖ Patients were considered to have a history of cardiovascular disease in the following cases: previous clinical or laboratory diagnosis of any form of structural heart disease, including ischemic heart disease, valvular dysfunction, and primary myocardial disease; previous diagnosis or clinical evidence of congestive heart failure; previous diagnosis or clinical evidence of peripheral arterial disease; or previous diagnosis of stroke or transient ischemic attack.
¶ Electrocardiogram tracings were considered abnormal in the following cases: rhythm abnormalities (atrial fibrillation or flutter, supraventricular tachycardia, multifocal atrial tachycardia, frequent or repetitive premature supraventricular or ventricular complexes, sustained or nonsustained ventricular tachycardia, paced rhythms); atrioventricular or intraventricular conduction disorders (complete atrioventricular block, Mobitz type I or Mobitz type II atrioventricular block, bundle branch block or intraventricular conduction delay); left or right ventricular hypertrophy; left axis deviation; old myocardial infarction; ST-segment and T wave abnormalities consistent with or possibly related to myocardial ischemia; or electrocardiographic recordings showing nonspecific repolarization abnormalities were not considered as abnormal.

and future measurements. High-sensitivity cTnI (hs-cTnI) measurements (part of the CSRS) were done using the ARCHITECT STAT High Sensitivity Troponin-I assay (Abbott Laboratories) (23), and hs-cTnT was measured using the Elecsys 2010 (Roche Diagnostics) (24). The hs-cTnI and hs-cTnT measurements were done blinded in a core laboratory. For the CSRS, which includes elevated cTn levels (>99th percentile) as a score item, study-specific hs-cTnI and hs-cTnT measurements done at the core laboratory were used, when available. In case study-specific hs-cTnI and hs-cTnT measurements were missing, cTn concentrations measured as part of routine clinical care were used. Also, if no clinical cTn concentrations were available, in accordance with the original CSRS studies (6, 7), cTn was imputed to normal.

Statistical Analysis

For the CSRS and OESIL score, we calculated the final point-based score for each patient in this cohort. That score, in combination with the reported intercept of the original derivation, was then used to calculate predicted probabilities of the original 30-day composite outcome for the CSRS (7). A recalibration was not done. For the OESIL score, because no intercept was reported in the original derivation study, a recalibration of the score was necessary before calculating predicted probabilities of the original OESIL 1-year mortality outcome (see section 2 of the **Supplement**, available at Annals.org) (25). We quantified discrimination by the area under the receiver-operating characteristic curves (AUCs) (26). Comparisons of correlated AUCs were done according to DeLong and colleagues (27). Calibration was assessed using calibration curves with a locally weighted smoothing algorithm, which offer a visualization of the agreement between observed and predicted probabilities of the outcome.

To examine the disposition decision capabilities of the CSRS and OESIL score, we created 3 comprehensive risk groups based on the original publications (7, 10): (very) low risk (CSRS ≤0, OESIL 0 to 1), medium risk (CSRS 1 to 3, OESIL 2), and (very) high risk (CSRS ≥4,

OESIL 3 to 4). Cox regression models and Kaplan–Meier curves were used to examine the incidence of composite outcomes over time and hazard ratios of patients stratified by the different risk groups, where the (very) low-risk group was used as reference for comparison (28). Individual analysis of the components of the CSRS in a multivariable regression model was done to assess consistency of their individual weight with the derivation cohort. Because the extent of work-up routinely done in the ED may be greater in countries other than Canada, the relative contribution of the clinician classification of syncope at ED discharge variable to the performance of the score may concurrently be higher in this study. Therefore, we compared the discrimination of the CSRS versus a simplified and refitted model on the basis of only the clinician classification of syncope at discharge. To compare the proportion of patients selected for discharge or admission from the ED by the CSRS versus the OESIL score versus the real-world ED decision, and adverse outcomes occurring in these patients, we created a contingency table stratified by admission status and risk categorization of the 2 scores. No formal sample size calculation was done because no universally accepted approach to sample size estimation is available for validation studies of risk prediction models. However, the number of patients and events or nonevents in this study far exceeds the common suggestion deduced from simulation studies of having at least 100 events and nonevents (29–32). Therefore, this analysis is expected to provide robust estimates (29–32). All hypothesis testing was 2-tailed; *P* values less than 0.05 were considered statistically significant. Statistical analyses were done using R, version 4.0 (R Foundation for Statistical Computing) (see section 3 of the **Supplement**, available at Annals.org).

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The funders had no role in the conduct of the study, analysis and interpretation of the data, drafting of the article, or the decision to submit the manuscript for publication.

RESULTS

Study Population

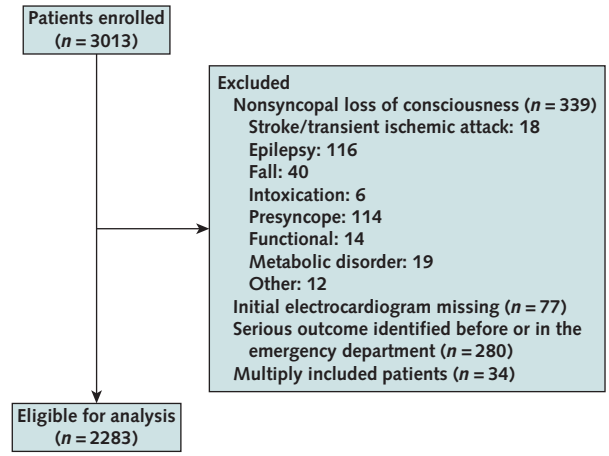
From May 2010 to October 2019, a total of 3013 patients were enrolled and had completed 12-month follow-up, of which 2283 were eligible for this analysis (**Figure 1**). Mean age was 68 years, 42% were women, and 19% had a history of coronary artery disease (**Table 2**). Overall, 54% of patients were hospitalized. The primary composite outcome at 30 days occurred in 7.2% (*n* = 165), and the composite outcome excluding procedural interventions occurred in 3.1% (*n* = 70) (**Table 3**). The score distribution of the CSRS and OESIL score across the cohort as well as 30-day event numbers and predicted probabilities of adverse outcomes by score are displayed in **Table 4**.

CSRS Performance and Comparison With the OESIL Score

Discrimination of the CSRS for the primary composite outcome at 30 days was good (AUC, 0.85 [95% CI, 0.83 to 0.88]) and was better than the OESIL score (AUC, 0.74 [CI, 0.71 to 0.78]; $P < 0.001$) (**Figure 2**, *left*). Similarly, discrimination of the CSRS for the composite outcome excluding procedural interventions (AUC, 0.80 [CI, 0.75 to 0.84]) was better than the OESIL score (AUC, 0.69 [CI, 0.64 to 0.75]; $P < 0.001$) (**Figure 2**, *right*). These findings were confirmed in a subgroup analysis stratifying patients by hospitalization status (**Supplement Figure 1**, available at Annals.org). Calibration of the CSRS and OESIL score (with a recalibrated intercept) overall was mostly suboptimal, except in the (very) low-risk group (**Figure 3**).

The CSRS triaged 60.8% (*n* = 1388) of patients toward (very) low risk; the OESIL score triaged 48.4% (*n* = 1104) of patients toward low risk. In these patients, the event rate for both composite outcomes at 30 days was lower with the CSRS versus the OESIL score (primary composite outcome: 15 of 1388 [1.1%] vs. 30 of 1104 [2.7%]; composite outcome excluding procedural interventions: 9 of 1388 [0.6%] vs. 17 of 1104 [1.5%]) (**Table 5** and **Figure 4**). Safety of triage toward (very) low risk using the CSRS was higher versus the OESIL score with, for example, a sensitivity of 91% (CI, 85% to 95%) versus 82% (CI, 75% to 87%) for the primary composite outcome at 30 days (**Supplement Table 1**, available at Annals.org).

Figure 1. Patient flow chart.



Serious outcome is defined as adverse event included in the study defined primary composite outcome or composite outcome excluding procedural interventions.

Comparison of the Disposition Decision According to CSRS Versus OESIL Score Versus Observed

Of 2283 patients, 45.9% or 1048 were observed to be discharged after ED evaluation by the treating physician in this study (**Supplement Table 2**, available at Annals.org); this is compared with 60.8% (1388 of 2283) identified as (very) low risk by the CSRS (absolute increase of 14.9% of patients), and 48.4% (1104 of 2282) identified as low risk by the OESIL score. Those classified as (very) low risk by the CSRS had lower rates of adverse outcomes than those discharged by the ED; compared

Table 2. Baseline Characteristics of the Study Population

Variable	Overall	30-Day Primary Composite Outcome			30-Day Composite Outcome Excluding Procedural Interventions		
		Without Event	With Event	*P* Value*	Without Event	With Event	*P* Value*
Patients, *total n* (%)†	2283 (100.0)	2118 (92.8)	165 (7.2)		2213 (96.9)	70 (3.1)	
Mean age (SD), *y*	68.1 (13.9)	67.5 (14.0)	76.6 (10.7)	<0.001	67.9 (14.0)	75.6 (11.1)	<0.001
Female, *n* (%)	949 (42)	887 (42)	62 (38)	0.29	917 (41)	32 (46)	0.54
Hospitalized, *n* (%)	1235 (54)	1087 (51)	148 (90)	<0.001	1176 (53)	59 (84)	<0.001
Characteristics of syncope, *n* (%)							
Nausea	686 (30)	652 (31)	34 (21)	0.010	669 (31)	17 (25)	0.35
Diaphoresis	762 (34)	742 (36)	20 (13)	<0.001	755 (35)	7 (10)	<0.001
Pallor	663 (44)	630 (45)	33 (31)	0.008	646 (44)	17 (44)	1.00
Palpitations	160 (7)	152 (7)	8 (5)	0.42	155 (7)	5 (8)	0.81
Angina pectoris	125 (6)	112 (5)	13 (8)	0.15	119 (5)	6 (9)	0.27
While supine	63 (3)	58 (3)	5 (3)	0.80	60 (3)	3 (4)	0.44
While sitting	907 (40)	853 (41)	54 (33)	0.057	888 (40)	19 (28)	0.034
While standing up	296 (13)	280 (13)	16 (10)	0.23	288 (13)	8 (12)	0.86
While standing	991 (44)	908 (43)	83 (51)	0.072	954 (43)	37 (54)	0.109
During exercise	172 (8)	146 (7)	26 (16)	<0.001	163 (7)	9 (13)	0.101
Medical history, *n* (%)							
Smoking	1120 (49)	1039 (49)	81 (51)	0.81	1088 (49)	32 (48)	0.81
Arterial hypertension	1352 (59)	1239 (59)	113 (68)	0.013	1309 (59)	43 (61)	0.81
Hypercholesterolemia	936 (42)	855 (41)	81 (49)	0.040	907 (42)	29 (42)	1.000
Diabetes mellitus	344 (15)	305 (14)	39 (24)	0.003	331 (15)	13 (19)	0.40
Coronary artery disease	423 (19)	367 (17)	56 (34)	<0.001	398 (18)	25 (36)	0.001
Myocardial infarction	242 (11)	208 (10)	34 (21)	<0.001	226 (10)	16 (23)	0.002
Congestive heart failure (New York Heart Association II-IV)	136 (6)	112 (5)	24 (15)	<0.001	124 (6)	12 (17)	0.001
Benign ventricular arrhythmia	435 (19)	380 (18)	55 (34)	<0.001	415 (19)	20 (29)	0.043
Pacemaker/cardiac resynchronization therapy/ implantable cardioverter-defibrillator device	109 (5)	100 (5)	9 (5)	0.70	101 (5)	8 (11)	0.017
Stroke	189 (8)	173 (8)	16 (10)	0.47	184 (8)	5 (7)	1.000
Medication, *n* (%)							
Aspirin	649 (28)	589 (28)	60 (36)	0.025	628 (28)	21 (30)	0.79
Anticoagulation	278 (12)	241 (11)	37 (22)	<0.001	262 (12)	16 (23)	0.009
Diuretic	645 (28)	573 (27)	72 (44)	<0.001	613 (28)	32 (46)	0.002
Digitalis	29 (1)	23 (1)	6 (4)	0.015	25 (1)	4 (6)	0.011
β-blocker	649 (28)	582 (27)	67 (41)	<0.001	621 (28)	28 (40)	0.042
Antiarrhythmic	72 (3)	63 (3)	9 (5)	0.099	70 (3)	2 (3)	1.000
Nitrate	114 (5)	102 (5)	12 (7)	0.190	108 (5)	6 (9)	0.160
Angiotensin-converting enzyme inhibitor/ angiotensin II antagonist	1001 (44)	903 (43)	98 (59)	<0.001	963 (44)	38 (54)	0.086
Calcium-channel blocker	374 (16)	350 (17)	24 (15)	0.59	366 (17)	8 (11)	0.33

* *P* values are for comparison between patients with and without 30-d adverse outcomes for both the primary composite as well as the composite outcome excluding procedural interventions.
† The *n* (%) in the first row (total *n*) denotes row percentages in respect to the total number of patients (*n* = 2283). All other *n* (%) denote column percentages in respect to the total number of the respective column excluding missing values per each variable.

with 1.6% of those who were discharged, only 1.1% of (very) low-risk patients by CSRS score had the primary composite outcome, and 0.6% (vs. 1.0%) had the composite outcome excluding procedural interventions at 30 days (Table 5; Supplement Table 3, available at Annals.org). In contrast, the incidence of both composite outcomes was higher in the low-risk group by OESIL (2.7% and 1.5%, respectively) than in those who were discharged (Table 5 and Supplement Table 3).

Contribution of Individual CSRS Components to Prognosis

Analysis of the 9 individual items of the CSRS in a multivariable regression model showed the largest odds ratios for clinician classification of syncope at ED discharge variable (cardiac syncope, vasovagal syncope, or other) in predicting the primary composite outcome at 30 days (Table 6). A simplified model including only the clinician classification of syncope variable achieved similar discrimination (AUC, 0.83 [CI, 0.80 to 0.87]) when compared with the entire CSRS (Figure 1).

Outcomes at 720 Days

Follow-up was complete in 2173 of 2283 patients (95.2%) at 720 days. Of 2283 patients, 472 (20.7%) developed the primary composite outcome, and 317 of 2283 (13.9%) patients developed the composite outcome excluding procedural interventions within 720 days. The event rate from day 31 to day 720 was lower compared with the event rate until day 30 in all 3 risk groups. However, the event rate remained higher in the (very) high-risk group compared with the medium-risk and (very) low-risk groups with continuously diverging survival curves (Supplement Figure 2, available at Annals.org).

Table 3. Serious Outcomes Within 30 and 720 Days After Disposition From the Emergency Department (Counting Only the First Event in Case of Multiple Events per Patient)

Serious Outcome	30 Days, *n* (%)*	720 Days, *n* (%)*
Death (all causes)	13 (7.9)	134 (28.5)
Arrhythmic outcomes		
Resuscitation	1 (0.6)	6 (1.3)
Life-threatening arrhythmia†	17 (10.3)	31 (6.6)
Pacemaker implantation‡	59 (35.8)	94 (20.0)
Implantable cardioverter-defibrillator implantation‡	14 (8.5)	17 (3.6)
Nonarrhythmic outcomes		
Acute coronary syndrome	11 (6.7)	39 (8.3)
Heart failure	8 (4.8)	46 (9.8)
Coronary revascularization (percutaneous transluminal coronary angioplasty or bypass surgery)‡	11 (6.7)	26 (5.5)
Valve intervention or surgery‡	11 (6.7)	18 (3.8)
Noncardiac outcomes		
Gastrointestinal bleeding	4 (2.4)	25 (5.3)
Intracranial bleeding	3 (1.8)	7 (1.5)
Severe bleeding requiring blood transfusion	4 (2.4)	7 (1.5)
Pulmonary embolism	7 (4.2)	15 (3.2)
Sepsis	2 (1.2)	7 (1.5)
Total primary composite outcome	165 (100)	472 (100)
Total composite outcome excluding procedural interventions	70	317

* The *n* (%) denotes column percentages in regard to the total number of the primary composite outcome.
† Life-threatening arrhythmia defined as ventricular fibrillation, sustained ventricular tachycardia (>120 beats/min), ventricular pause (>3 s), or ventricular standstill and asystole.
‡ Interventional procedures not included in the composite outcome excluding procedural interventions.

DISCUSSION

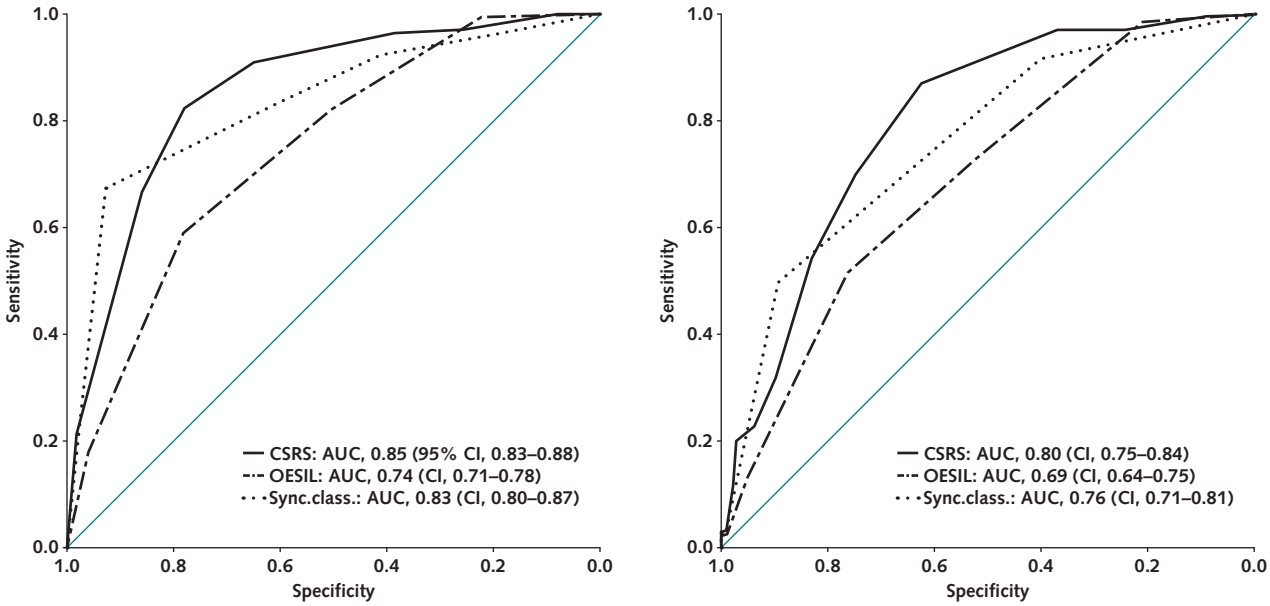
This is the first large international validation of the CSRS. We report 4 major findings. First, prognostic discrimination of the CSRS was good for predicting adverse clinical outcomes. Second, by applying the CSRS, more than half of patients (60.8%) were triaged to the (very) low-risk group, in whom hospitalization often may not be necessary. In contrast, more than 1 in 3 patients in this low-risk subgroup were hospitalized. Less than 1% of patients identified as (very) low risk by the CSRS had adverse clinical outcomes at 30 days. Third, although the CSRS did significantly better in predicting 30-day adverse outcomes not evident during index ED evaluation compared with the OESIL score, the performance of

Table 4. Distribution of CSRS and OESIL Scores*

Score	Patients, *n* (%)	Risk Category	30-Day Primary Composite Outcome, *n* (%) [95% CI]	30-Day Composite Outcome Excluding Procedural Interventions, *n* (%) [95% CI]	Predicted Probability (95% CI), %
CSRS					
−3	153 (6.7)	Very low	0 (0.0) [0.0–2.4]	0 (0.0) [0.0–2.4]	0.5 (0.2–1.3)
−2	399 (17.5)	Very low	5 (1.3) [0.5–2.9]	2 (0.5) [0.1–1.8]	0.8 (0.5–1.4)
−1	272 (11.9)	Low	1 (0.4) [0.1–2.1]	0 (0.0) [0.0–1.4]	1.3 (0.5–3.4)
0	564 (24.7)	Low	9 (1.6) [0.8–3.0]	7 (1.2) [0.6–2.5]	2.1 (2.1–2.1)
1	291 (12.7)	Medium	14 (4.8) [2.9–7.9]	12 (4.1) [2.4–7.1]	3.4 (2.3–5.1)
2	194 (8.5)	Medium	26 (13.4) [9.3–18.9]	11 (5.7) [3.2–9.9]	5.4 (3.9–8.7)
3	166 (7.3)	Medium	36 (21.7) [16.1–28.6]	16 (9.6) [6–15.1]	8.6 (4.4–19.5)
4	93 (4.1)	High	21 (22.6) [15.3–32.1]	6 (6.5) [3.0–13.4]	13.5 (13.7–71.5)
5	76 (3.3)	High	18 (23.7) [15.5–34.4]	2 (2.6) [0.7–9.1]	20.4 (15.3–86.4)
6	29 (1.3)	Very high	16 (55.2) [37.5–71.6]	8 (27.6) [14.7–45.7]	29.7 (10.8–92.3)
7	26 (1.1)	Very high	12 (46.2) [28.8–64.5]	4 (15.4) [6.2–33.5]	41.1 (10.9–96.9)
8	12 (0.5)	Very high	2 (16.7) [4.7–44.8]	0 (0.0) [0.0–24.2]	53.5 (32.2–99.7)
9	8 (0.4)	Very high	5 (62.5) [30.6–86.3]	2 (25.0) [7.1–59.1]	65.5 (32.4–99.9)
10	0	Very high	–	–	–
11	0	Very high	–	–	–
OESIL					
0	474 (20.8)	Low	1 (0.2) [0–1.2]	1 (0.2) [0–1.2]	0.9 (0.9–0.9)
1	630 (27.6)	Low	29 (4.6) [3.2–6.5]	16 (2.5) [1.6–4.1]	2.4 (2.0–5.6)
2	622 (27.2)	Medium	38 (6.1) [4.5–8.3]	17 (2.7) [1.7–4.3]	6.3 (4.1–20.6)
3	444 (19.4)	High	68 (15.3) [12.3–19]	27 (6.1) [4.2–8.7]	15.4 (5.4–40.7)
4	113 (4.9)	High	29 (25.7) [18.5–34.4]	9 (8) [4.2–14.4]	33.1 (5.7–59.2)

CSRS = Canadian Syncope Risk Score; OESIL = Osservatorio Epidemiologico della Sincope nel Lazio.
* Presented with associated risk categories as well as the number, proportion, and 95% CI of recorded serious outcomes for the 30-d primary composite outcome as well as the 30-d composite outcome excluding procedural interventions and predicted probabilities with 95% CIs for each score. Patients *n* (%) denotes column percentages of total *n* = 2283. All other *n* (%) denote row percentages in regard to patients per score.

Figure 2. The AUCs displaying the prognostic discrimination of the CSRS, OESIL score, and the simplified model based only on the sync.class. at ED discharge for both the primary composite outcome (*left*) and the composite outcome excluding procedural interventions (*right*) at 30 days.



AUC = area under the receiver-operating characteristic curve; CSRS = Canadian Syncope Risk Score; OESIL = Osservatorio Epidemiologico della Sincope nel Lazio; sync.class. = clinician classification of syncope.

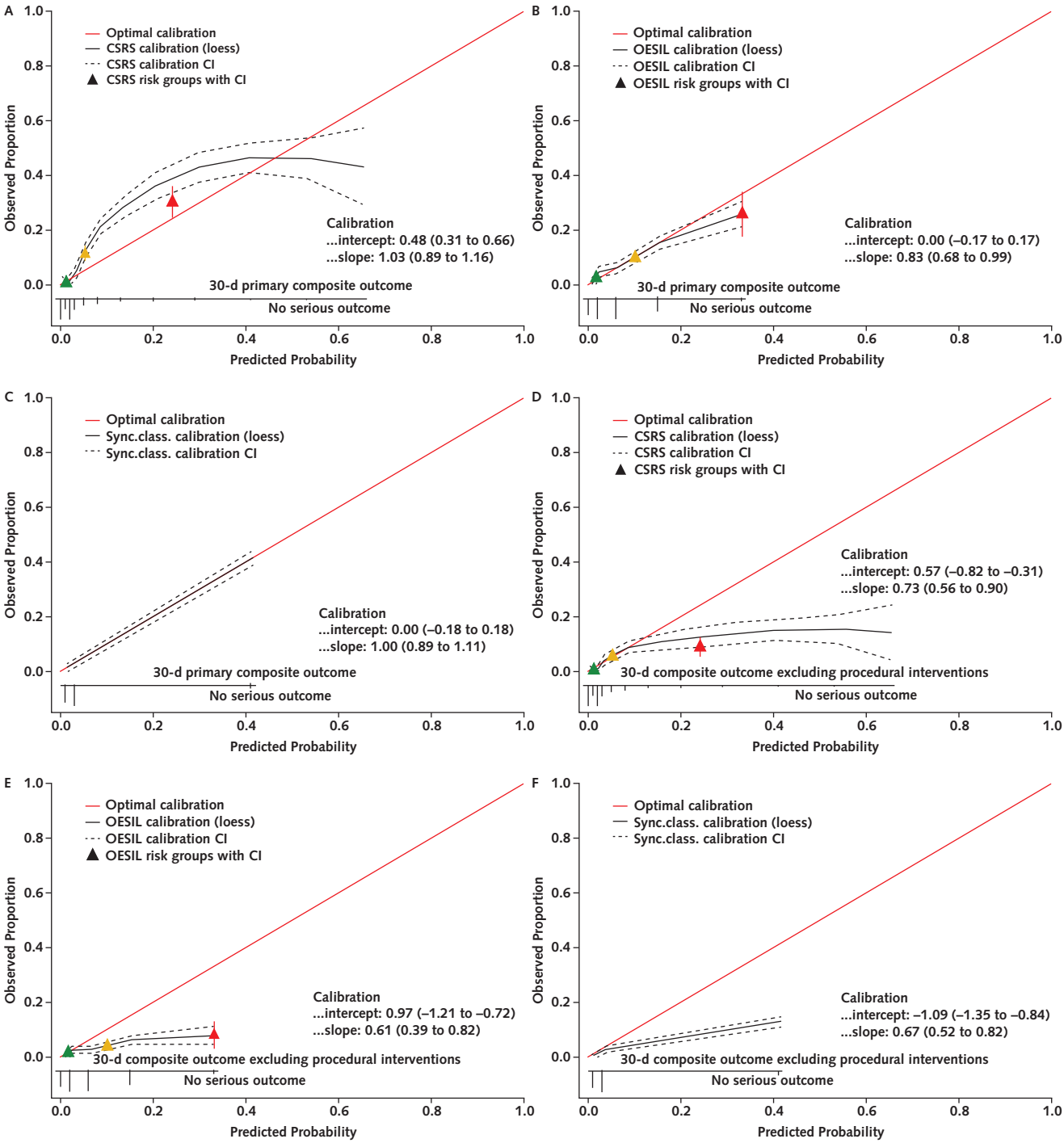
the CSRS was mainly driven by clinician classification of syncope (cardiac syncope, vasovagal syncope, or other) at ED discharge. Given that a simplified model based only on this syncope classification variable achieved similar discrimination versus the CSRS, the incremental clinical value of the CSRS is likely marginal in EDs with a similar standard of care to the 14 EDs across 8 countries contributing to this study. Fourth, analysis of long-term follow-up confirmed the validity of the 3 risk groups and the increased risk for patients in the medium-risk and (very) high-risk groups even over 720 days.

This study corroborates and extends the previous findings of the Canadian derivation study and the national validation study showing high prognostic accuracy (AUC, 0.88 [CI, 0.85 to 0.90] and 0.91 [CI, 0.88 to 0.93], respectively) in a younger population (mean age of 54 years for both studies) with a lower prevalence of known cardiac disorders to an older and more international population in our study (mean age, 68 years) (6, 7). A national Italian multicenter validation study found moderate prognostic accuracy of the CSRS (AUC, 0.75 [CI, 0.68 to 0.81]) in a small cohort (n = 345), with a median age of 71 years (18). Another small (n = 283) single-center cohort from Australia with a mean age of 56 years recorded only 7 serious adverse events within 30 days and found modest performance of the CSRS (19). None of the 2 studies reported data on calibration (18, 19). Although the national Canadian validation study found an optimal calibration of the CSRS, we found good calibration only for the (very) low-risk group without refitting the model but using the originally derived data to calculate probabilities in our cohort. Similar results were shown for the calibration of the OESIL score, refitted on our cohort. The suboptimal calibration of the medium-risk and high-risk groups, however, may be of less clinical relevance because the primary aim was to focus on the identification of patients at low risk to allow safe discharge. As the uncertainty about patient disposition increases with patient age because of the increase in the prevalence of a cardiac cause of syncope, the patient population enrolled in this study seems to represent well those patients in whom clinicians perceive the need for help in determining the right disposition decision after ED evaluation (1, 3).

It is unknown why the 9 items of the CSRS had a rather balanced contribution to its performance in the Canadian derivation study, whereas in this large international study, the performance of the CSRS was mainly driven by the final clinician classification of syncope. It is conceivable that the extent of work-up done in the ED may have been different in our study, and the corresponding diagnostic accuracy of the syncope classification by the treating physician at the end of ED evaluation may have contributed to this discrepancy.

Substantial variations in admission rates seen in different health care systems ranging from 12% in parts of Canada to 54% in this study and as much as 80% in U.S. centers (16, 17) suggest that not only medical factors but also social, financial, and legal concerns may play a role in disposition decisions. Given recent evidence that a large proportion of admissions is likely inappropriate and sometimes even harmful, current clinical practice guidelines highlight the need for strategies to reduce admissions for syncope (1, 2, 15, 33). The economic effect of implementing strategies for improved risk stratification and more

Figure 3. Calibration plots for the CSRS (*A*), OESIL score (*B*), and sync.class. (*C*) for the 30-day primary composite outcome as well as the 30-day composite outcome excluding procedural interventions (CSRS [*D*], OESIL score [*E*], and sync.class. [*F*]) using a loess algorithm displaying predicted (x-axis) versus observed (y-axis) probabilities.



Probabilities were predicted on the basis of the total score of each patient and the originally derived intercept for the CSRS and the total score of each patient and the recalibrated intercept for the OESIL score. The recalibration of the OESIL score and the refitting of the model on the basis of the sync. class. does not allow a comparison of calibration between the scores. Triangles mark the average of the 3 risk groups (green = [very] low risk, orange = medium risk, and red = [very] high risk). CSRS = Canadian Syncope Risk Score; loess = locally weighted smoothing; OESIL = Osservatorio Epidemiologico della Sincope nel Lazio; sync.class. = clinician classification of syncope.

Table 5. Stratification by Observed Admission Decisions (Hospitalized Vs. Discharged) and Risk Categories of the CSRS and OESIL Score for the Primary Composite Outcome and the Composite Outcome Excluding Procedural Interventions at 30 Days*

Outcome	Patients/Events	(Very) Low Risk, % (*n*/*N*)		Not Low Risk, % (*n*/*N*)		Total, % (*n*/*N*)
		CSRS	OESIL	CSRS	OESIL	
30-d primary composite outcome						
Hospitalized	Patients	25.7 (586/2283)	19.7 (450/2283)	28.4 (649/2283)	34.4 (785/2283)	54.1 (1235/2283)
	Events	1.7 (10/586)	5.6 (25/450)	21.3 (138/649)	15.7 (123/785)	12.0 (148/1235)
Discharged	Patients	35.1 (802/2283)	28.6 (654/2283)	10.8 (246/2283)	17.3 (394/2283)	45.9 (1048/2283)
	Events	0.6 (5/802)	0.8 (5/654)	4.9 (12/246)	3.0 (12/394)	1.6 (17/1048)
Total	Patients	60.8 (1388/2283)	48.4 (1104/2283)	39.2 (895/2283)	51.6 (1179/2283)	100.0 (2283/2283)
	Events	1.1 (15/1388)	2.7 (30/1104)	16.8 (150/895)	11.5 (135/1179)	100.0 (165/165)
30-d composite outcome excluding procedural interventions						
Hospitalized	Patients	25.7 (586/2283)	19.7 (450/2283)	28.4 (649/2283)	34.4 (785/2283)	54.1 (1235/2283)
	Events	1.0 (6/586)	3.1 (14/450)	8.2 (53/649)	5.7 (45/785)	4.8 (59/1235)
Discharged	Patients	35.1 (802/2283)	28.6 (654/2283)	10.8 (246/2283)	17.3 (394/2283)	45.9 (1048/2283)
	Events	0.4 (3/802)	0.5 (3/654)	3.3 (8/246)	2.0 (8/394)	1.0 (11/1048)
Total	Patients	60.8 (1388/2283)	48.4 (1104/2283)	39.2 (895/2283)	51.6 (1179/2283)	100.0 (2283/2283)
	Events	0.6 (9/1388)	1.5 (17/1104)	6.8 (61/895)	4.5 (53/1179)	100.0 (70/70)

CSRS = Canadian Syncope Risk Score; OESIL = Osservatorio Epidemiologico della Sincope nel Lazio.
* Only patients in the (very) low risk group are applicable for potential discharge, whereas patients in the medium and (very) high risk groups, summarized here as "not low risk," are suggested to receive further work-up and/or admission.

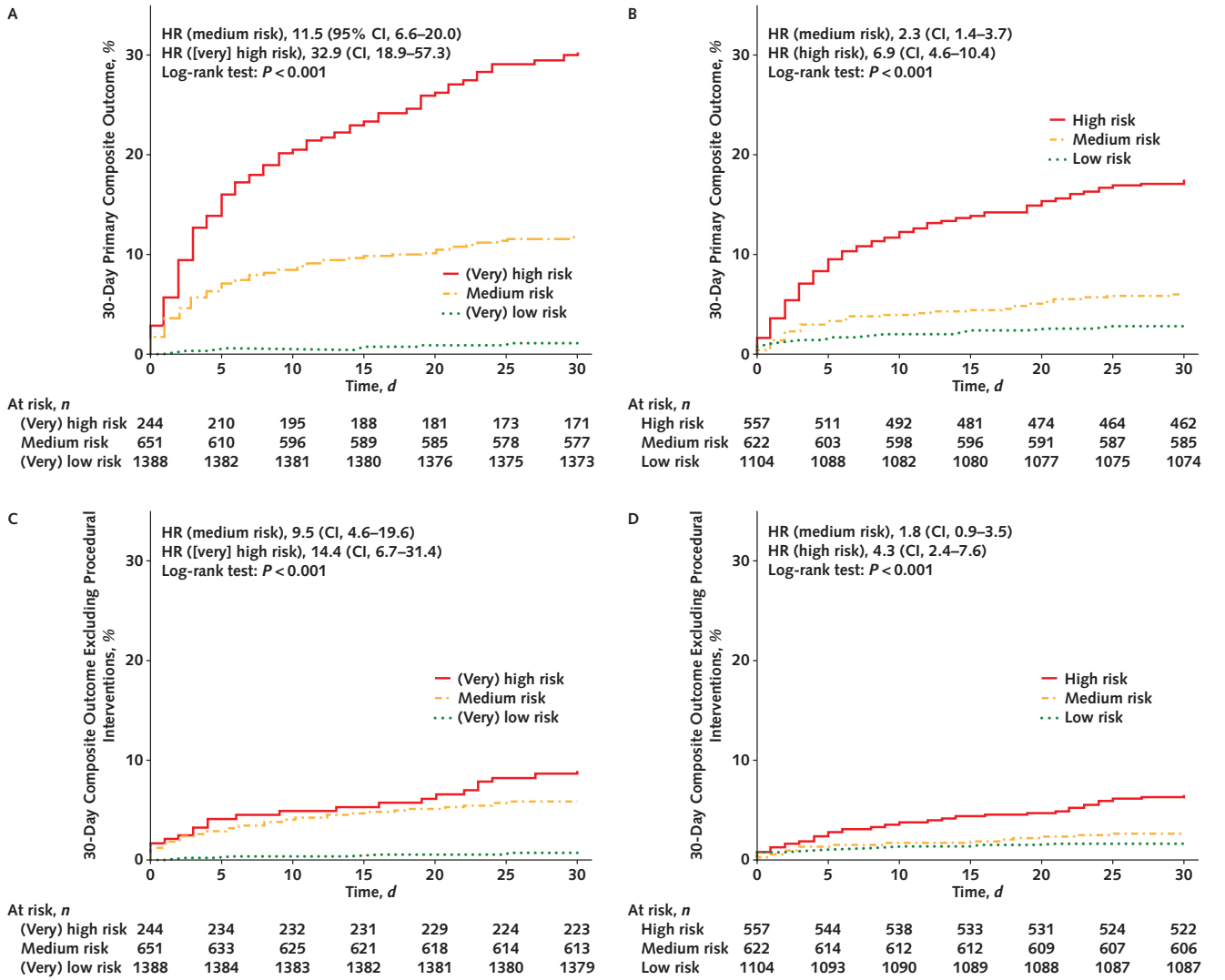
tailored hospitalizations could be substantial (8). Given the average cost of hospitalization for syncope of around $8700, an estimated 1.5 million patients presenting to the ED with syncope in the United States and Europe annually (1, 2, 8, 34), reduction in the rate of hospitalization from 60% to 50% by the improved identification of patients at low risk could result in health care savings of more than $1.3 billion in the United States and Europe alone.

All elements of the CSRS and OESIL score, including clinician classification of syncope (part of the CSRS but not OESIL) are part of the established ED work-up in most institutions. Therefore, feeding back the results to the physicians could easily occur in time for the disposition decision. Using the CSRS to identify low-risk patients for ED discharge could reduce hospitalizations with a lower adverse event rate in those discharged. Despite its moderate performance in this cohort, the OESIL score may still be preferred in some institutions because it includes fewer and equally weighted variables (4 vs. 9 in CSRS), allowing easier bedside use even without an online calculator. Furthermore, because the OESIL score does not include clinician classification of syncope (that is, physician judgment), it is not expected to do as well as the CSRS. However, by only including objective values, the OESIL score is less dependent on the experience and acumen of the treating physician, whereas the performance of the CSRS is highly dependent on the physician using the score, making it unlikely to reproduce consistent performance in even similar settings. However, those classified as low risk by OESIL had a higher event rate than those discharged from the ED by clinicians in this study. To answer the questions of how well the CSRS would do without the physician judgment and how it would then compare with the OESIL score, the CSRS would have to be rederived and recalibrated without the clinician classification of syncope component, which is beyond the scope of this study but is a potential future direction for research.

Future studies are also warranted to address open questions about the clinical implementation of the CSRS, which also apply to the OESIL score. First, the preferred threshold for risk used to select patients eligible for outpatient management may differ among different health care settings and depend on the risk tolerance for adverse outcomes and the acceptable tradeoffs between appropriate hospitalizations of those at risk and unnecessary hospitalization of those at low risk. Hospitalization may have other benefits, such as intensified monitoring and work-up, which can lead to more rapid diagnosis and initiation of therapy. Thereby, hospitalization may improve more downstream health outcomes not captured in this study. Second, about one third of patients were triaged by the CSRS to the medium-risk group. The disposition and extent of monitoring that best balances safety and economic needs in this group largely remain unknown.

Several limitations of this study merit consideration. First, 54% of patients in this international multicenter study were admitted. Because the intensity of monitoring is higher during hospitalization and some procedures included in the primary composite outcome can only be done when the patient is hospitalized and may be driven by the clinician's classification of syncope after ED evaluation, inclusion of the syncope classification variable could introduce ascertainment and incorporation bias—because this variable affects the score but also affects the procedural outcome. This may lead to an overestimation of the performance of the CSRS in the primary outcome, which included procedural interventions. Therefore, it is important to highlight that the good prognostic discrimination of the CSRS was confirmed in

Figure 4. Kaplan-Meier curves showing the incidence of the primary composite outcome for the CSRS (*A*) and OESIL score (*B*) as well as the composite outcome excluding procedural interventions (CSRS [*C*] and OESIL score [*D*]) at 30 days.



The graphs are stratified by the 3 risk groups: (very) low risk (CSRS ≤0, OESIL 0 to 1, green/dotted), medium risk (CSRS 1 to 3, OESIL 2, orange/dashed), and (very) high risk (CSRS ≥4, OESIL 3 to 4, red/solid). The HRs are calculated with (very) low risk as the reference group. The log-rank test compares survival distributions between risk groups. CSRS = Canadian Syncope Risk Score; HR = hazard ratio; OESIL = Osservatorio Epidemiologico della Sincope nel Lazio.

predicting adverse events when these procedural interventions were excluded from the composite outcome. Second, in most centers, patient enrollment was done by study-specific staff, with most patients being enrolled during the day and in the evening. Therefore, this study, like most previous studies on syncope, has an underrepresentation of patients presenting during the night. However, syncopal events occurring at night overall seem to have similar characteristics to those occurring during the daytime (35). Third, because our study mostly included older patients (mean age, 68 years), generalizability to younger patients is unclear. International validation of the CSRS in younger patients is still pending.

In conclusion, in this international external validation study, the CSRS showed good performance in the identification of patients at low risk for serious outcomes and, therefore, possible candidates for discharge from the ED and was superior to the OESIL score. However, because clinician classification of syncope seemed to drive much of the performance of the CSRS, the incremental value and clinical utility of the CSRS remains unclear and warrants further study, preferably in the form of a randomized controlled trial.

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Table 6. Multivariable Logistic Regression Model for the 30-Day Primary Composite Outcome With CSRS and OESIL Score Predictors

Predictor	β Coefficient	Odds Ratio (95%CI)
CSRS		
Predisposition to vasovagal syncope	−0.58	0.56 (0.32–0.96)
History of heart disease	0.28	1.33 (0.89–1.97)
Systolic blood pressure reading <90 or > 180 mm Hg	0.11	1.12 (0.55–2.28)
Elevated troponin level (>99th percentile)	0.20	1.22 (0.77–1.92)
Abnormal QRS axis (<−30° or >110°)	0.41	1.48 (0.94–2.39)
QRS duration >130 ms	0.75	2.12 (1.22–3.67)
Corrected QT interval >480 ms	0.15	1.16 (0.69–1.94)
Clinician classification of syncope (ED diagnosis) as vasovagal syncope	−0.82	0.44 (0.23–0.83)
Clinician classification of syncope (ED diagnosis) as cardiac syncope	2.79	16.30 (10.75–24.71)
Intercept	−3.58	
AUC	0.88 (0.85–0.91)	
OESIL		
Age >65 y	1.34	3.85 (2.28–6.50)
History of cardiovascular disease	0.64	1.89 (1.35–2.65)
Syncope without prodrome	0.40	1.49 (1.05–2.12)
Abnormal electrocardiogram	1.10	3.01 (2.06–4.40)
Intercept	−4.65	
AUC	0.76 (0.72–0.79)	

AUC = area under the receiver-operating characteristic curve; CSRS = Canadian Syncope Risk Score; ED = emergency department; OESIL = Osservatorio Epidemiologico della Sincope nel Lazio.

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References

1. **Brignole M, Moya A, de Lange FJ, et al; ESC Scientific Document Group.** 2018 ESC guidelines for the diagnosis and management of syncope. Eur Heart J. 2018;39:1883-1948. [PMID: 29562304] doi:10.1093/eurheartj/ehy037

2. **Shen WK, Sheldon RS, Benditt DG, et al.** 2017 ACC/AHA/HRS guideline for the evaluation and management of patients with

syncope: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2017;70:620-663. [PMID: 28286222] doi:10.1016/j.jacc.2017.03.002
3. **Olde Nordkamp LR, van Dijk N, Ganzeboom KS, et al.** Syncope prevalence in the ED compared to general practice and population: a strong selection process. Am J Emerg Med. 2009;27:271-9. [PMID: 19328369] doi:10.1016/j.ajem.2008.02.022
4. **du Fay de Lavallaz J, Badertscher P, Nestelberger T, et al.** B-type natriuretic peptides and cardiac troponins for diagnosis and risk-stratification of syncope. Circulation. 2019;139:2403-2418. [PMID: 30798615] doi:10.1161/CIRCULATIONAHA.118.038358
5. **Derose SF, Gabayan GZ, Chiu VY, et al.** Patterns and preexisting risk factors of 30-day mortality after a primary discharge diagnosis of syncope or near syncope. Acad Emerg Med. 2012;19:488-96. [PMID: 22594351] doi:10.1111/j.1553-2712.2012.01336.x
6. **Thiruganasambandamoorthy V, Sivilotti MLA, Le Sage N, et al.** Multicenter emergency department validation of the Canadian Syncope Risk Score. JAMA Intern Med. 2020;180:737-744. [PMID: 32202605] doi:10.1001/jamainternmed.2020.0288
7. **Thiruganasambandamoorthy V, Kwong K, Wells GA, et al.** Development of the Canadian Syncope Risk Score to predict serious adverse events after emergency department assessment of syncope. CMAJ. 2016;188:E289-E298. [PMID: 27378464] doi:10.1503/cmaj.151469
8. **Sun BC.** Quality-of-life, health service use, and costs associated with syncope. Prog Cardiovasc Dis. 2013;55:370-5. [PMID: 23472773] doi:10.1016/j.pcad.2012.10.009
9. **Martin TP, Hanusa BH, Kapoor WN.** Risk stratification of patients with syncope. Ann Emerg Med. 1997;29:459-66. [PMID: 9095005]
10. **Colivicchi F, Ammirati F, Melina D, et al; OESIL (Osservatorio Epidemiologico sulla Sincope nel Lazio) Study Investigators.** Development and prospective validation of a risk stratification system for patients with syncope in the emergency department: the OESIL risk score. Eur Heart J. 2003;24:811-9. [PMID: 12727148]
11. **Costantino G, Perego F, Dipaola F, et al; STePS Investigators.** Short- and long-term prognosis of syncope, risk factors, and role of hospital admission: results from the STePS (Short-Term Prognosis of Syncope) study. J Am Coll Cardiol. 2008;51:276-83. [PMID: 18206736] doi:10.1016/j.jacc.2007.08.059
12. **Probst MA, Gibson T, Weiss RE, et al.** Risk stratification of older adults who present to the emergency department with syncope: the FAINT score. Ann Emerg Med. 2020;75:147-158. [PMID: 31668571] doi:10.1016/j.annemergmed.2019.08.429
13. **Quinn JV, Stiell IG, McDermott DA, et al.** Derivation of the San Francisco Syncope Rule to predict patients with short-term serious outcomes. Ann Emerg Med. 2004;43:224-32. [PMID: 14747812]
14. **Reed MJ, Newby DE, Coull AJ, et al.** The ROSE (Risk stratification Of Syncope in the Emergency department) study. J Am Coll Cardiol. 2010;55:713-21. [PMID: 20170806] doi:10.1016/j.jacc.2009.09.049
15. **Costantino G, Casazza G, Reed M, et al.** Syncope risk stratification tools vs clinical judgment: an individual patient data meta-analysis. Am J Med. 2014;127:1126.e13-1126.e25. [PMID: 24862309] doi:10.1016/j.amjmed.2014.05.022
16. **Birnbaum A, Esses D, Bijur P, et al.** Failure to validate the San Francisco Syncope Rule in an independent emergency department population. Ann Emerg Med. 2008;52:151-9. [PMID: 18282636] doi:10.1016/j.annemergmed.2007.12.007
17. **Thiruganasambandamoorthy V, Hess EP, Alreesi A, et al.** External validation of the San Francisco Syncope Rule in the Canadian setting. Ann Emerg Med. 2010;55:464-72. [PMID: 19944489] doi:10.1016/j.annemergmed.2009.10.001
18. **Solbiati M, Talerico G, Villa P, et al.** Multicentre external validation of the Canadian Syncope Risk Score to predict adverse events and comparison with clinical judgement. Emerg Med J. 2021;38:701-706. [PMID: 34039646] doi:10.1136/emermed-2020-210579
19. **Chan J, Ballard E, Brain D, et al.** External validation of the Canadian Syncope Risk Score for patients presenting with undifferentiated syncope to the emergency department. Emerg Med Australas. 2021;33:418-424. [PMID: 33052034] doi:10.1111/1742-6723.13641
20. **Collins GS, Reitsma JB, Altman DG, et al; members of the TRIPOD group.** Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): the TRIPOD statement. Eur Urol. 2015;67:1142-1151. [PMID: 25572824] doi:10.1016/j.eururo.2014.11.025
21. **du Fay de Lavallaz J, Badertscher P, Nestelberger T, et al; BASEL IX Investigators.** Prospective validation of prognostic and diagnostic syncope scores in the emergency department. Int J Cardiol. 2018;269:114-121. [PMID: 30224031] doi:10.1016/j.ijcard.2018.06.088
22. **Leitch JW, Klein GJ, Yee R, et al.** Syncope associated with supraventricular tachycardia: an expression of tachycardia rate or vasomotor response. Circulation. 1992;85:1064-71. [PMID: 1537103]
23. **Krintus M, Kozinski M, Boudry P, et al.** European multicenter analytical evaluation of the Abbott ARCHITECT STAT high sensitive troponin I immunoassay. Clin Chem Lab Med. 2014;52:1657-65. [PMID: 24897400] doi:10.1515/cclm-2014-0107
24. **Giannitsis E, Kurz K, Hallermayer K, et al.** Analytical validation of a high-sensitivity cardiac troponin T assay. Clin Chem. 2010;56:254-61. [PMID: 19959623] doi:10.1373/clinchem.2009.132654
25. **Janssen KJ, Moons KG, Kalkman CJ, et al.** Updating methods improved the performance of a clinical prediction model in new patients. J Clin Epidemiol. 2008;61:76-86. [PMID: 18083464]
26. **Steyerberg EW, Van Calster B, Pencina MJ.** Performance measures for prediction models and markers: evaluation of predictions and classifications. Rev Esp Cardiol. 2011;64:788-94. [PMID: 21763052] doi:10.1016/j.recesp.2011.04.017
27. **DeLong ER, DeLong DM, Clarke-Pearson DL.** Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics. 1988;44:837-45. [PMID: 3203132]
28. **Cox DR.** Regression models and life-tables. J R Stat Soc Series B Stat Methodol. 1972;34:187-202.
29. **Vergouwe Y, Steyerberg EW, Eijkemans MJ, et al.** Substantial effective sample sizes were required for external validation studies of predictive logistic regression models. J Clin Epidemiol. 2005;58:475-83. [PMID: 15845334]
30. **Collins GS, Ogundimu EO, Altman DG.** Sample size considerations for the external validation of a multivariable prognostic model: a resampling study. Stat Med. 2016;35:214-26. [PMID: 26553135] doi:10.1002/sim.6787
31. **Moons KG, Altman DG, Reitsma JB, et al.** Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. Ann Intern Med. 2015;162:W1-73. [PMID: 25560730] doi:10.7326/M14-0698
32. **Puhan MA, Hansel NN, Sobradillo P, et al; International COPD Cohorts Collaboration Working Group.** Large-scale international validation of the ADO index in subjects with COPD: an individual subject data analysis of 10 cohorts. BMJ Open. 2012;2:e002152. [PMID: 23242246] doi:10.1136/bmjopen-2012-002152
33. **Canzoniero JV, Afshar E, Hedian H, et al.** Unnecessary hospitalization and related harm for patients with low-risk syncope. JAMA Intern Med. 2015;175:1065-7. [PMID: 25894921] doi:10.1001/jamainternmed.2015.0945
34. **Probst MA, Kanzaria HK, Gbedemah M, et al.** National trends in resource utilization associated with ED visits for syncope. Am J Emerg Med. 2015;33:998-1001. [PMID: 25943042] doi:10.1016/j.ajem.2015.04.030
35. **du Fay de Lavallaz J, Badertscher P, Nestelberger T, et al; BASEL IX Investigators.** Circadian, weekly, seasonal, and temperature-dependent patterns of syncope aetiology in patients at increased risk of cardiac syncope. Europace. 2019;21:511-521. [PMID: 30137300] doi:10.1093/europace/euy186

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