External Validation of the San Francisco Syncope Rule

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Study objective: We externally validate the ability of the San Francisco Syncope Rule to accurately identify syncope patients who will experience a 7-day serious clinical event.

Methods: Patients who presented to a single academic emergency department (ED) between 8 AM and 10 PM with syncope or near-syncope were prospectively enrolled. Treating physicians recorded the presence or absence of all San Francisco Syncope Rule risk factors. Patients were contacted by telephone at 14 days for a structured interview. A 3-physician panel, blinded to the San Francisco Syncope Rule score, reviewed ED medical records, hospital records, and telephone interview forms to identify predefined serious clinical events. The primary outcome was the ability of the San Francisco Syncope Rule to predict any 7-day serious clinical event. A secondary outcome was the ability of the San Francisco Syncope Rule to predict 7-day serious clinical events that were not identified during the initial ED evaluation.

Results: Of 592 eligible patients, 477 (81%) provided informed consent. Direct telephone contact or admission/outpatient records were successfully obtained for 463 (97%) patients. There were 56 (12%) patients who had a serious 7-day clinical event, including 16 (3%) who received a diagnosis after the initial ED evaluation. Sensitivity and specificity of the San Francisco Syncope Rule for the primary outcome were 89% (95% confidence interval [CI] 81% to 97%) and 42% (95% CI 37% to 48%), respectively, and 69% (95% CI 46% to 92%) and 42% (95% CI 37% to 48%), respectively, for the secondary outcome. Estimates of sensitivity were minimally affected by missing data and most optimistic assumptions for missing follow-up information.

Conclusion: In this external validation cohort, the San Francisco Syncope Rule had a lower sensitivity and specificity than in previous reports. [Ann Emerg Med. 2007;49:420-427.]

INTRODUCTION

Background and Importance

Syncope, defined as a transient loss of consciousness, may herald life-threatening events. As a result, patients presenting with syncope to emergency departments (EDs) are frequently hospitalized. Syncope accounts for 1% to 3% of all ED visits and hospital admissions from the ED. Unfortunately, current admission practices result in marginal diagnostic and therapeutic benefit and consume enormous health care resources. Between 39% and 50% of admitted patients are discharged without an explanation for syncope, and syncope-related admissions in the United States account for $2.4 billion in annual health care costs.

The San Francisco Syncope Rule is an instrument designed to identify patients with syncope or near-syncope who are at low risk of a short-term, serious clinical event. Low-risk patients can potentially be discharged for an outpatient evaluation of syncope. The San Francisco Syncope Rule predictors include an abnormal ECG result, complaint of shortness of breath, hematocrit level less than 30%, systolic blood pressure less than 90 mm Hg, and a history of congestive heart failure.
In a derivation study, outcomes included any predefined clinical events within 7 days; the San Francisco Syncope Rule demonstrated 96% sensitivity (95% confidence interval [CI] 92% to 100%) and 62% specificity (95% CI 58% to 66%).

In a validation study, outcomes included 30-day predefined events that were diagnosed after the ED visit; the San Francisco Syncope Rule demonstrated 98% sensitivity (95% CI 89% to 100%) and 56% specificity (95% CI 52% to 60%).

Goals of This Investigation

The published San Francisco Syncope Rule derivation and validation studies have been performed at the same institution. Our goal was to evaluate the accuracy of the San Francisco Syncope Rule to identify “low-risk” patients in an independent, prospective validation sample. The primary outcome included all 7-day serious clinical events. The secondary outcome included 7-day serious clinical events that were diagnosed only after the index ED visit. Analysis of the secondary outcome is important because there is little clinical utility in “predicting” serious conditions that are evident at the ED evaluation.

MATERIALS AND METHODS

Study Design and Setting

This was a single-center, prospective, observational, cohort study that enrolled patients from April 18, 2005, to April 18, 2006. The study site is an urban, academic, Level I trauma center with an emergency medicine residency and an annual volume of 40,000 visits. The study site institutional review board approved the research protocol.

Selection of Participants

Adult patients with a complaint of syncope or near-syncope were eligible for enrollment. Syncope is defined as a sudden, transient loss of consciousness. Near-syncope is defined as a sensation of imminent loss of consciousness, without actual syncope. The treating resident or attending physician determined patient eligibility for study enrollment.

Exclusion criteria included loss of consciousness related to a witnessed seizure, loss of consciousness after head trauma, ongoing confusion (including baseline cognitive impairment or dementia), intoxication, age younger than 18 years, inability to speak English or Spanish, do-not-resuscitate (DNR) or do-not-intubate (DNI) status, and lack of follow-up contact information.

An ED-based research assistant was available from 8 AM to 10 PM, 7 days a week. Research assistants identified all potentially eligible patients by reviewing the ED intake log and querying the charge nurse, attending physicians, and resident physicians as they were evaluating active ED patients. A research assistant explained the goals of the study to eligible patients and obtained informed consent for enrollment. Retrospective internal quality checks, including medical record review and ED intake log review, demonstrated that 76% of eligible patients were identified and screened. There were no differences in age and sex among potentially eligible patients who were screened and those who were not screened.

All elements of the San Francisco Syncope Rule were collected prospectively. For each enrolled patient, the treating resident emergency physician completed a structured data form about that patient’s clinical presentation (Appendix E1 available online at http://www.annemergmed.com). Presence of shortness of breath, history of congestive heart failure, or abnormal ECG result was obtained from the physician structured data form. For shortness of breath and history of congestive heart failure, the treating physician could record “yes,” “no,” or “unknown.” The ECG was considered abnormal if the treating physician noted it to show any rhythm other than sinus, any bundle-branch block, left-axis deviation, mono- or biventricular hypertrophy, any abnormal conduction interval except for first-degree atrioventricular block, any Q/ST/T change consistent with ischemia (acute or chronic), or isolated, nonspecific ST/T abnormalities. A research assistant verified completeness of data forms and abstracted triage systolic blood pressure from nursing notes. Hematocrit values were obtained from a computerized laboratory reporting system. Information about age, sex, race, and ethnicity were obtained from administrative data.

The clinical evaluation data forms were completed by emergency medicine residents with 2 to 4 years of experience. To assess the interrater reliability of clinical predictors and to assess San Francisco Syncope Rule accuracy as a function of
clinician experience, the attending emergency physician independently completed a second data form in a convenience sample of patients. The research assistant requested that the attending physician complete a second form for all patients; however, attending physicians were occasionally unable to complete the form because of other clinical responsibilities. Attending and resident physicians were trained in the completion of the data forms in 1 session before and 1 session after initiation of the study. Physicians were instructed to treat and admit patients in their usual manner, without any specific study intervention or testing.

For patients who did not receive ECG testing as part of routine care, a research assistant obtained patient permission to perform a study ECG. Study ECGs were immediately sealed, were not available to treating physicians, and were interpreted later by a study investigator (B.C.S.) who was blinded to other information about the patient’s presentation. Hematocrit testing was performed at the discretion of treating physicians, and we did not collect hematocrit data if this test was not ordered as part of routine care.

The primary outcome included all 7-day predefined serious clinical events. The secondary outcome included 7-day serious clinical events that were diagnosed only after the initial ED evaluation.

Predefined outcomes included death, myocardial infarction, arrhythmias, pulmonary embolism, stroke or transient ischemic attack, subarachnoid or nontraumatic cerebral hemorrhage, aortic dissection, new diagnosis of structural heart disease thought to be related to syncope, and significant hemorrhage or anemia requiring blood transfusion. Explicit criteria were used to identify outcomes (Appendix E2, available online at http://www.annemergmed.com). Any patient who was discharged from the ED or hospital after an episode of syncope and then readmitted for similar symptoms related to the initial event was considered to have a serious outcome. Admitted patients who required a predefined acute intervention during their stay were also considered to have a serious outcome. An acute intervention was defined as a procedure required to treat a condition related to a patient’s symptoms of syncope, including pacemaker insertion, coronary angioplasty, surgery for valvular heart disease, balloon pump insertion, use of vasopressors, surgery to treat an abdominal aortic aneurysm surgery for ruptured spleen, surgery for ruptured ectopic pregnancy, and endoscopic treatment of esophageal varices. Our outcomes definitions are consistent with those used by the San Francisco Syncope Rule investigators, and the outcomes period is consistent with that of the original derivation study.

Outcomes Measurement

Direct patient telephone follow-up was performed to identify admissions or serious clinical events that occurred outside the study site. We attempted to contact all patients at 14 days after the index ED visit for a structured telephone interview by a research assistant (Appendix E3, available online at http://www.annemergmed.com). Inpatient records and discharge summaries were obtained for all patients transferred from the study site ED to other hospitals for admission.

Two emergency physicians independently reviewed available ED documentation, inpatient records, and telephone interview forms for all enrolled patients. Records for all patients identified as potentially experiencing a serious outcome were then reviewed by a panel of 3 emergency physicians. All reviewing physicians were blinded to the structured data forms completed by treating physicians. Occurrence and timing of the predefined, serious clinical events were determined through panel consensus and recorded on a structured data form (Appendix E4, available online at http://www.annemergmed.com).

According to published data, we assumed that the San Francisco Syncope Rule would have a sensitivity of 98%. Power analyses suggested that approximately 50 enrolled patients with the primary outcome would be required to achieve a 95% CI width of 10%.

Primary Data Analysis

We performed descriptive analysis of baseline patient characteristics stratified by occurrence of a serious outcome. Between-group differences and CIs in characteristics were estimated using Wilson estimates for binomial variables. The κ statistic was used to assess the interrater reliability of clinical predictors.

In the base case analysis, we analyzed all patients who either had the presence of at least 1 of the 5 high-risk predictors (because these patients were classified as “at risk” regardless of missing data on other predictors) or who had complete data on all 5 predictors recorded on the form (completed by a resident physician). For shortness of breath and history of congestive heart failure, we treated a response of “unknown” as missing data. ECG data were considered missing if an ECG was not ordered by the treating physician and a study ECG was not performed. Hematocrit data were considered missing if this test was not ordered by the treating physician. We determined sensitivity, specificity, negative predictive value, and positive predictive value of the San Francisco Syncope Rule to identify patients with all 7-day outcomes, as well as 7-day outcomes that were diagnosed after the initial ED evaluation. In this base case subgroup, we compared the San Francisco Syncope Rule test characteristics with physician judgment, which we defined as the treating physicians’ decision to hospitalize the patient.

Sensitivity Analyses

We performed sensitivity analyses to assess the impact of missing data. We estimated the upper bounds of sensitivity by assuming that all missing data represented the absence of a predictor. To estimate the upper bounds of specificity, we assumed that all missing data represented the presence of a predictor. We compared the results of these sensitivity analyses against the treating physician’s judgment in the entire study cohort.
We also assessed the potential impact of missing follow-up information, again in a manner that would estimate the maximal sensitivity and specificity of the San Francisco Syncope Rule. We made the following assumptions for patients without follow-up information: (1) for patients with at least 1 San Francisco Syncope Rule high-risk predictor or who had complete data on all San Francisco Syncope Rule predictors, we assumed that the patient experienced the outcome predicted by the San Francisco Syncope Rule; and (2) for patients with missing data on the San Francisco Syncope Rule predictors and who did not have at least 1 San Francisco Syncope Rule predictor, we assumed that the patient did not experience a serious outcome.

We repeated the analysis described above using clinical evaluation data completed by attending physicians.

Data management and statistical analyses were conducted using SAS software, version 8.02 (SAS Institute Inc., Cary, NC). Test characteristics and associated 95% CIs were calculated using a publicly available SAS macro.14

RESULTS

Of the 709 patients who were screened during the study period, 592 (83%) were eligible, and 477 (81%) provided informed consent to participate. We found no important differences in age, sex, race, or ethnicity between eligible patients who provided or declined informed consent. Direct telephone follow-up was obtained in 436 patients (91%). Of the remaining 41 patients, 27 (6% of the entire cohort) had available inpatient or outpatient data for at least 2 weeks after the date of enrollment, and 14 (3%) had no available follow-up information. Patients without any available follow-up information were younger and more likely to be of nonwhite race compared with patients with follow-up information. Study sample characteristics are presented in Table 1.

Study sample characteristics are presented in Table 1. Of the overall cohort, 58% were admitted or transferred to another hospital. Blood pressure data were available for all patients, and data were missing in less than 1.5% of patients for presence of

Table 1. Study population characteristics.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (n=477), %</th>
<th>No Serious Event (n=421), %</th>
<th>7-Day Serious Event (n=56), %</th>
<th>Difference Between Groups (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median, y (IQR)</td>
<td>58 (35, 79)</td>
<td>55 (32, 78)</td>
<td>76 (60, 85)</td>
<td>24 (9 to 40)</td>
</tr>
<tr>
<td>&lt;40</td>
<td>30</td>
<td>33</td>
<td>7</td>
<td>5 (7 to 17)</td>
</tr>
<tr>
<td>40-59</td>
<td>23</td>
<td>24</td>
<td>18</td>
<td>-15 (-26 to -5)</td>
</tr>
<tr>
<td>60-79</td>
<td>24</td>
<td>22</td>
<td>38</td>
<td>-17 (-27 to -7)</td>
</tr>
<tr>
<td>&gt;80</td>
<td>21</td>
<td>21</td>
<td>38</td>
<td>-24 (-35 to -13)</td>
</tr>
<tr>
<td>Male</td>
<td>44</td>
<td>41</td>
<td>66</td>
<td>-2 (-10 to 6)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>10</td>
<td>10</td>
<td>11</td>
<td>8 (-18 to 1)</td>
</tr>
<tr>
<td>White</td>
<td>77</td>
<td>76</td>
<td>86</td>
<td>5 (-4 to 13)</td>
</tr>
<tr>
<td>Black</td>
<td>9</td>
<td>10</td>
<td>11</td>
<td>1 (-10 to 7)</td>
</tr>
<tr>
<td>Asian</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>2 (-3 to 7)</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>37</td>
</tr>
<tr>
<td>Disposition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admitted</td>
<td>51</td>
<td>45</td>
<td>93</td>
<td>46 (-54 to -39)</td>
</tr>
<tr>
<td>Transferred</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>-1 (-8 to 6)</td>
</tr>
<tr>
<td>Discharged</td>
<td>40</td>
<td>45</td>
<td>0</td>
<td>44 (25 to 62)</td>
</tr>
<tr>
<td>Left against medical advice</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>1 (-4 to 5)</td>
</tr>
<tr>
<td>SF SR predictors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal ECG</td>
<td>37</td>
<td>32</td>
<td>73</td>
<td>-41 (-50 to -32)</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>12</td>
<td>11</td>
<td>20</td>
<td>-10 (-18 to -2)</td>
</tr>
<tr>
<td>Hematocrit &lt;30</td>
<td>6</td>
<td>4</td>
<td>15</td>
<td>-12 (-17 to -8)</td>
</tr>
<tr>
<td>SBP &lt;90 mm Hg</td>
<td>5</td>
<td>5</td>
<td>9</td>
<td>-5 (-11 to 1)</td>
</tr>
<tr>
<td>History of CHF</td>
<td>8</td>
<td>7</td>
<td>16</td>
<td>-10 (-17 to -3)</td>
</tr>
<tr>
<td>Any SF SR predictor</td>
<td>46</td>
<td>41</td>
<td>89</td>
<td>-46 (-53 to -38)</td>
</tr>
</tbody>
</table>

IQR, Interquartile range; SBP, systolic blood pressure; CHF, congestive heart failure; SFSR, San Francisco Syncope Rule.

*Subgroups may not add to exactly 100% because values are rounded to the nearest integer.

†Represents group difference of (no serious event)–(serious event); point estimates are based on Wilson estimates and may not be exactly the same as the absolute difference of group proportions.
shortness of breath (n=7) or history of congestive heart failure (n=6). Less than 7% of patients did not receive an ECG as part of routine care and refused a study ECG (n=33). Finally, 32% of patients did not receive hematocrit testing as part of routine care (n=153).

The proportion of patients with any 7-day serious clinical event was 11.7% (56 of 477 patients), and the proportion of patients with a 7-day serious clinical event that was diagnosed only after the index ED visit was 3.4% (16 of 477 patients). Serious clinical events are described in Table 2.

Second rater evaluation forms were completed by an attending physician. The Figure describes patients who present between 10PM and 8AM. Interrater reliability for presence of shortness of breath, abnormal ECG, and presence of any San Francisco Syncope Rule predictor was modest (Table 3).

Table 4 presents the test characteristics of the San Francisco Syncope Rule under various assumptions. In the base case analysis, a decision by the managing physicians to admit the patient was 100% sensitive and 30% specific for all 7-day outcomes. The point estimates for San Francisco Syncope Rule sensitivity were 89% for any 7-day serious event and 69% for a 7-day serious event that was diagnosed only after the initial ED visit. If patients without San Francisco Syncope Rule risk factors were discharged and all others admitted, hospitalizations would have decreased in the base case subgroup by 12%, but at the price of having discharged 5 patients (10% of primary outcomes) who would have subsequently been diagnosed with a serious event.

Estimates of sensitivity were minimally affected by missing data on the San Francisco Syncope Rule predictors, whereas estimates of specificity depended on how missing data were handled. San Francisco Syncope Rule test characteristics were minimally affected by missing follow-up information when the most optimistic assumptions were used. Point estimates for sensitivity and specificity were lower when elements of the San Francisco Syncope Rule were calculated from forms completed by an attending physician. The Figure describes patients who were misclassified as “low risk” by the San Francisco Syncope Rule in the base case analysis.

LIMITATIONS

We performed a prospective cohort study designed to minimize missing data bias and maximize direct patient follow-up with a standardized protocol. Nevertheless, there are potential limitations to our study.

We excluded children, patients with DNR/DNI status, and patients without follow-up contact information, whereas these were not exclusion criteria used by the San Francisco Syncope Rule investigators. It is possible that the San Francisco Syncope Rule demonstrated different test characteristics in these patients.

We did not enroll patients between 10 PM and 8 AM, for logistic reasons, and this may be a source of selection bias. We did not detect age or sex differences between eligible patients during study hours and patients with a chief complaint of “syncope” who presented after study hours, although we did not have data to perform a more detailed analysis of differences between the 2 groups. However, we have no reason to believe that the San Francisco Syncope Rule would have different test characteristics in patients who present between 10 PM and 8 AM.

We successfully screened 76% of potentially eligible patients during study hours. Most of the potentially eligible patients who were not screened were missed because of research assistant unavailability (eg, multiple patients requiring screening at the same time, or gaps in research assistant coverage schedule). Although we did not find a difference in age and sex between potentially eligible patients who were screened and those who were not, this may be a source of selection bias.

We collected data on triage blood pressure and did not have data on other recorded blood pressure measurements during the ED visit. Clinicians may be influenced by the lowest measured blood pressure value, and future studies should explore the importance of serial blood pressure measurements.

ECG and hematocrit testing were not available in 7% and 32% of enrolled patients, respectively. Of patients with a 7-day serious outcome, all but 1 patient received an ECG, and all received hematocrit testing. A 21-year-old man diagnosed with upper gastrointestinal bleeding and a hematocrit level of 22% did not receive ECG testing. Thus, such missing data could not substantially affect our estimates of sensitivity, whereas it tends to provide an upwardly biased estimate of specificity because of

<table>
<thead>
<tr>
<th>Type of Event†</th>
<th>All 7-Day Events No. (%)</th>
<th>“Delayed” 7-Day Events No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arhythmia</td>
<td>32 (57)</td>
<td>7 (44)</td>
</tr>
<tr>
<td>Hemorrhage/anemia</td>
<td>8 (14)</td>
<td>0</td>
</tr>
<tr>
<td>Structural heart disease</td>
<td>6 (11)</td>
<td>3 (19)</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>2 (4)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Pacemaker placement</td>
<td>2 (4)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>PTCA</td>
<td>2 (4)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Aortic dissection</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>56</td>
<td>16</td>
</tr>
</tbody>
</table>

*Some patients experienced more than 1 event; this table classifies patients by the first clinically observed event.
†Denominator is total number of patients experiencing an event; columns may not add to exactly 100% because values are rounded to the nearest integer.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Subgroup No.</th>
<th>Percentage Agreement</th>
<th>K (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shortness of breath</td>
<td>288</td>
<td>90</td>
<td>0.5 (0.3–0.6)</td>
</tr>
<tr>
<td>Abnormal ECG</td>
<td>241</td>
<td>75</td>
<td>0.5 (0.4–0.6)</td>
</tr>
<tr>
<td>Any high-risk predictor*</td>
<td>225</td>
<td>85</td>
<td>0.6 (0.5–0.7)</td>
</tr>
</tbody>
</table>

*Observations were dropped if either rater did not complete all elements of the SFSR and no abnormal findings were present.
the potential for false-positive test results, which is supported by results of our preplanned sensitivity analysis assessing the effects of missing data.

Our definition of an abnormal ECG was slightly different from that used by the San Francisco Syncope Rule investigators. The San Francisco Syncope Rule derivation study considered an ECG with new changes to be abnormal. We did not have uniform data on past ECGs on enrolled patients; therefore, any predefined findings on ECG were considered abnormal, regardless of past ECG testing. Therefore, our estimates of sensitivity are likely to be biased upward and specificity downward because of this measurement difference, although the effect size of this variation is likely minimal.

We used outcomes as defined by the original San Francisco Syncope Rule derivation study, including all 7-day predefined, serious clinical events. In their validation study, however, the San Francisco Syncope Rule investigators used a different outcomes definition, which included 30-day serious clinical events that were diagnosed after the initial ED presentation. In pilot work, we found an unacceptable decrease in telephone interview response rate when the follow-up period was extended from 14 to 30 days. Therefore, we cannot assess the exact outcome used in the validation study reported by the San Francisco Syncope Rule validation study. In post hoc analysis to assess the impact of measuring a longer period, however, we found no qualitative differences in San Francisco Syncope Rule sensitivity estimates when we used a 14-day period for all serious events, as well as events that were diagnosed after the initial ED visit.

This was a single-center study, and it is possible that the San Francisco Syncope Rule demonstrates different test characteristics when applied by physicians at other institutions. Finally, we observed a relatively small number of serious events in our study cohort, and a larger study with more outcomes would provide narrower 95% CIs for estimates of San Francisco Syncope Rule sensitivity and specificity.

### DISCUSSION

We performed a prospective cohort study to externally validate the San Francisco Syncope Rule. Study strengths

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#### Table 4. San Francisco Syncope Rule test characteristics with likelihood ratios.

<table>
<thead>
<tr>
<th>Assumption</th>
<th>No.</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Positive Predictive Value (95% CI)</th>
<th>Negative Predictive Value (95% CI)</th>
<th>Likelihood Ratio Positive</th>
<th>Likelihood Ratio Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>All 7-day serious outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physician decision to admit, base case*</td>
<td>351</td>
<td>100 (94–100)</td>
<td>30 (25–35)</td>
<td>21 (16–26)</td>
<td>100 (96–100)</td>
<td>1.4</td>
<td>0</td>
</tr>
<tr>
<td>SFSR base case*</td>
<td>351</td>
<td>89 (81–97)</td>
<td>42 (37–48)</td>
<td>22 (17–28)</td>
<td>95 (92–99)</td>
<td>1.5</td>
<td>0.3</td>
</tr>
<tr>
<td>Physician decision to admit, all patients</td>
<td>477</td>
<td>100 (94–100)</td>
<td>47 (42–51)</td>
<td>20 (19–25)</td>
<td>100 (98–100)</td>
<td>1.9</td>
<td>0</td>
</tr>
<tr>
<td>SFSR missing predictors set to “present”</td>
<td>477</td>
<td>89 (81–97)</td>
<td>30 (25–34)</td>
<td>15 (11–18)</td>
<td>95 (92–99)</td>
<td>1.3</td>
<td>0.4</td>
</tr>
<tr>
<td>SFSR missing predictors set to “absent”</td>
<td>477</td>
<td>88 (79–96)</td>
<td>59 (55–64)</td>
<td>22 (17–28)</td>
<td>97 (95–99)</td>
<td>2.1</td>
<td>0.2</td>
</tr>
<tr>
<td>“Delayed” 7-day serious outcomes (exclude 40 patients with serious events diagnosed during ED evaluation)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SFSR base case*</td>
<td>311</td>
<td>69 (46–92)</td>
<td>42 (37–48)</td>
<td>6 (3–10)</td>
<td>96 (93–100)</td>
<td>1.2</td>
<td>0.7</td>
</tr>
<tr>
<td>SFSR missing predictors set to “present”</td>
<td>437</td>
<td>69 (46–92)</td>
<td>30 (25–34)</td>
<td>4 (2–6)</td>
<td>96 (93–99)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>SFSR missing predictors set to “absent”</td>
<td>437</td>
<td>69 (46–92)</td>
<td>59 (55–64)</td>
<td>6 (3–10)</td>
<td>98 (96–100)</td>
<td>1.7</td>
<td>0.5</td>
</tr>
<tr>
<td>All 7-day serious outcomes, best case assumptions for missing follow-up information†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SFSR base case*</td>
<td>361</td>
<td>90 (83–98)</td>
<td>45 (40–51)</td>
<td>26 (20–32)</td>
<td>96 (92–99)</td>
<td>1.6</td>
<td>0.2</td>
</tr>
<tr>
<td>All 7-day serious outcomes, worst case assumptions for missing follow-up information†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SFSR base case*</td>
<td>361</td>
<td>75 (63–84)</td>
<td>42 (36–48)</td>
<td>22 (17–29)</td>
<td>88 (81–93)</td>
<td>1.3</td>
<td>0.6</td>
</tr>
<tr>
<td>All 7-day serious outcomes, resident and attending evaluations available</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SFSR base case, attending physicians*</td>
<td>206</td>
<td>81 (69–94)</td>
<td>32 (25–39)</td>
<td>20 (14–27)</td>
<td>89 (81–97)</td>
<td>1.2</td>
<td>0.6</td>
</tr>
<tr>
<td>SFSR base case, residents*</td>
<td>206</td>
<td>89 (79–99)</td>
<td>40 (32–47)</td>
<td>25 (17–32)</td>
<td>94 (89,100)</td>
<td>1.5</td>
<td>0.3</td>
</tr>
</tbody>
</table>

*Includes patients for whom an SFSR score could be calculated.
†See Materials and Methods section for description of assumptions.
include a protocol to minimize missing ECG data, high rates of
direct patient follow-up, a physician outcomes review panel that
was blinded to data recorded by treating physicians, and explicit
methods for assessing the effects of missing data on San
Francisco Syncope Rule predictors and missing follow-up
information. At our institution, physician application of the San
Francisco Syncope Rule demonstrated lower sensitivity and
specificity than previously reported.12,13 In particular, the San
Francisco Syncope Rule demonstrated poor sensitivity for
identifying patients with a serious event that was first diagnosed
after the initial ED visit. Estimates of sensitivity were minimally
affected by missing ECG and hematocrit data, whereas estimates
of specificity depended on how missing data were analyzed. Test
characteristics were minimally affected by missing follow-up
information under the most optimistic assumptions. Treating
physicians admitted all patients who developed a 7-day serious
event. Application of the San Francisco Syncope Rule in this
study cohort could have reduced hospitalizations by 12%, but at
the price of missing 10% of patients with a 7-day serious
outcome.

Two previous syncope risk prediction instruments focused
on 1-year outcomes, including death or arrhythmias.15,16 Risk
prediction for 1-year outcomes, however, is unlikely to be
helpful for ED decisionmaking about whether to acutely
hospitalize a patient. A recent study reported a risk score for
predicting arrhythmias in patients with unexplained syncope,
hospitalize a patient. A recent study reported a risk score for
helpful for ED decisionmaking about whether to acutely
prediction for 1-year outcomes, however, is unlikely to be
sensory.

The San Francisco Syncope Rule represents a potentially
important advance in syncope risk stratification for emergency
physicians because of its focus on short-term serious events for
which hospitalization may be beneficial. The San Francisco
Syncope Rule investigators have reported the results of a
derivation and validation study. The derivation study included
684 enrolled patients, and 79 (11.5%) experienced a 7-day
serious event. The San Francisco Syncope Rule demonstrated
96% sensitivity (95% CI 92% to 100%) and 62% specificity
(95% CI 58% to 66%). The proportion of patients with a
serious event that was diagnosed after the initial ED evaluation
was not reported for the derivation study. The validation study
included 791 patients, and 54 (6.8%) experienced a 30-day
serious event after their initial ED visit. The San Francisco
Syncope Rule demonstrated 98% sensitivity (95% CI 89% to
100%) and 56% specificity (95% CI 52% to 60%) in the
validation study. ECG and hematocrit testing, 2 of the San
Francisco Syncope Rule predictors, were not mandatory in
either the San Francisco Syncope Rule derivation or validation
study, and it is unclear how frequently these tests were ordered
and how missing data affected the reported results.

The lower sensitivity and specificity of the San Francisco
Syncope Rule noted in our study may have several explanations.
First, physicians at our site may be unskilled in applying the San
Francisco Syncope Rule criteria. The criteria are relatively
simple, however, and we did provide 2 training sessions to train
study site physicians in the completion of the data form. We did
not find that the San Francisco Syncope Rule test characteristics
improved when applied by attending physicians compared to
resident physicians. Second, it is possible that San Francisco
Syncope Rule accuracy varies by patient population. Our study
site is an academic, tertiary-care referral center that treats many
patients with complex medical conditions. However, the San
Francisco Syncope Rule was derived and validated at a center
with similar characteristics. Third, because of the relatively small
number of patients who experienced a serious event in our
study, there are fairly wide CIs around our point estimates for
sensitivity and specificity. CIs for sensitivity overlap from our
study and the San Francisco Syncope Rule derivation and
validation reports. However, our findings suggest that the San
Francisco Syncope Rule may require further validation before
safe clinical application.

We propose the following recommendations for future
syncope risk stratification research. First, research should focus
on short-term serious events that are diagnosed after the initial
ED visit. In our cohort, internal hemorrhage and anemia were
always diagnosed in the ED, whereas undeclared outcomes
included only cardiac and neurologic events. Narrowing the
scope of outcomes may result in a more accurate and clinically
intuitive prediction instrument.

Second, future studies should include sufficient numbers of
serious events to allow for robust multivariate risk prediction
analysis. Because the rate of delayed serious events is low
(approximately 3% at 7 days in our study), an adequately
powered study may require thousands of patients.

Finally, older patients (age >60 years) accounted for the
majority of serious events in our cohort, as well as the majority
of serious outcomes missed by the San Francisco Syncope Rule.
Although other investigators have found age to be a powerful
predictor of syncope-related adverse events,15-20 the San
Francisco Syncope Rule does not include age as a risk factor.
The importance of age as a risk predictor should be reevaluated
in future studies. An ideal study setting for further risk
stratification research would be a large, population-based,
closed-cohort system, with older patients accounting for a high
proportion of syncope-related ED visits.

In summary, we performed an external validation study of
the San Francisco Syncope Rule. In our cohort, the San
Francisco Syncope Rule displayed lower sensitivity and
specificity for 7-day serious events than previously reported.
Point estimates of sensitivity were minimally affected by missing
data. Test characteristics were minimally affected by missing
follow-up information under the most optimistic assumptions.
Our results suggest that further validation studies should be
performed before widespread implementation of the San
Francisco Syncope Rule.

We are indebted to the efforts of the University of California, Los
Angeles emergency medicine research associates who performed
patient enrollment, data entry, and telephone follow-up interviews.
We also thank the residents, faculty, and nursing staff who cared for these patients and completed the data forms.

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Author contributions: BCS, CMM, JRH, and WRM conceived the study, BCS and CMM obtained funding for this study. BCS, GM, TW, GZS, GZ, and SS were responsible for data collection, and BCS supervised the overall data collection process. BCS performed the data analysis and drafted the article. All authors contributed substantially to article revisions. BCS takes responsibility for the paper as a whole.

Michael Callaham, MD, recused himself from the editorial decision process for this article.

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REFERENCES


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Appendix E1. Data Collection Form*

**HISTORY OF PRESENT ILLNESS:** Current syncopal episode:
Associated with shortness of breath  □ Yes  □ No  □ Unknown

**PAST MEDICAL HISTORY:**
Congestive heart failure  □ Yes  □ No  □ Unknown

**ECG :**
□ ECG performed as part of routine care  □ ECG not performed as part of routine care

ECG Interpretation (If sealed study ECG, leave this section blank and do not unseal ECG):
□ Normal: includes sinus tachycardia, first degree block, sinus bradycardia>50, premature atrial contractions
□ Isolated, nonspecific ST/T abnormalities
□ Abnormal. Check all the following that apply:
  □ Non-sinus rhythms  □ Bundle branch block  □ Left axis deviation  □ LVH/RVH
  □ Abnormal conduction intervals excluding first degree block
  □ Q/ST/T changes consistent with acute or chronic ischemia
  □ Other- describe:

*This is an abbreviated version of the data collection form that includes variables relevant for this report.
Appendix E2. Explicit Criteria for Outcomes.

Anhymia
- Ventricular tachycardia >3 beats
- Sick sinus disease, with alternating sinus bradycardia and tachycardia
- Sinus pause >3 s
- Third-degree atrioventricular block
- Mobitz II atrioventricular block
- Symptomatic supraventricular tachycardia (pulse rate >100 beats/min)
- Symptomatic atrial flutter or fibrillation with rapid ventricular response (pulse rate >100 beats/min)
- Symptomatic bradycardia (pulse rate <60 beats/min), OR pulse rate <40.
- “Symptomatic” refers to the simultaneous occurrence of dizziness, lightheadedness, hypotension (systolic blood pressure <90), or syncope with an arrhythmia on ECG monitoring.

Myocardial Infarction
- Requires increase of troponin or ECG change AND
- Documentation that cardiology consultation concurs with diagnosis of myocardial infarction

Stroke/TIA
- Requires increase of troponin or ECG change AND
- Documentation that cardiology consultation concurs with diagnosis of myocardial infarction

Pulmonary Embolism
- Requires confirmatory testing (high-probability VQ scan, chest CTA, pulmonary angiography, or new deep vein thrombosis noted on duplex ultrasonography WITH an abnormal VQ scan OR abnormal chest CTA OR abnormal pulmonary angiography)

Aortic Dissection
- Requires confirmatory testing (chest CT, transesophageal echocardiogram, MRI, or angiography)

Subarachnoid or Intracranial Hemorrhage (Nontraumatic)
- Requires that neurology or neurosurgical consultation concur with diagnosis

Internal Hemorrhage/Anemia Requiring Transfusion
- Any source of bleeding (GI, vaginal, ruptured AAA) or anemia requiring blood transfusion (includes patients who refuse recommended transfusion, eg, Jehovah’s witnesses)
Appendix E3. Contact script for telephone interview.

Hello, Mr./Mrs. __________________, my name is ______________. I work with Dr. XXXXXXX at XXXXXXX Emergency Medicine Center. You have previously agreed to participate in our survey when you were seen on ______________ (date of enrollment) at the XXXXXXX Medical Center Emergency Department. Please know that it is your right to decline to participate in this study for any reason, at any time. In addition, whether you decide to participate or not will not affect any aspect of your medical care.

Would you like to take part in this final portion of the study?
Do you have any questions or concerns I can address for you about the study?

If study participant answers affirmatively to participation, then request study related questions as follows:

____________________________

Did you return to the hospital or were you seen by a healthcare provider after discharge from the XXXXXXX Medical Center?

☐ Yes  ☐ No  ☐ Patient died

(If no: “Thank you for your time. Good bye.”)

Were you admitted to a hospital?
(explain):__________________

☐ Yes  ☐ No  ☐ Unknown

If you were admitted, which hospital were you admitted to?

____________________________

When were you admitted?

____________________________

Have you received any medical procedures since your visit to the emergency department (for example, heart catheterization, heart surgery, pacemaker placement, colonoscopy)?

☐ Yes  ☐ No

If yes, what procedure:__________________

Where was the procedure performed?__________________

Have you had any new medication started or medications changed since your visit to the emergency department (for example, heart medications, blood thinners, antibiotics)?

☐ Yes  ☐ No

If yes, please describe:__________________

Who is the physician who recommended the medication?__________________

What institution is that physician affiliated with?__________________

“Thank you so much for your participation.”
Appendix E4. Adverse Event Form.

**Adverse Events**

Did the patient develop any of the following adverse events on 14 day followup (check boxes that apply- indicate number of days after ED presentation that adverse event occurred- use 0 if adverse event was noted in the initial emergency department evaluation)?

- ☐ Death If yes, days after initial ED evaluation: 
  Indicate presumed cause of death: ☐ Sudden ☐ Cardiac ☐ Non-Cardiac
- ☐ Arrhythmia: specify type If yes, days after initial ED evaluation:
  - ☐ Ventricular tachycardia ☐ PSVT (includes PAT) ☐ Mobitz II or Type III block
  - ☐ Atrial fibrillation/flutter ☐ Bradycardia ☐ Sick sinus syndrome
  - ☐ Other
- ☐ Myocardial Infarction If yes, days after initial ED evaluation:
- ☐ Acute pulmonary edema If yes, days after initial ED evaluation:
- ☐ Stroke/TIA If yes, days after initial ED evaluation:
- ☐ Pulmonary embolism If yes, days after initial ED evaluation:
- ☐ Aortic dissection If yes, days after initial ED evaluation:
- ☐ Clinically significant structural heart disease If yes, days after initial ED evaluation:
  Indicate condition (e.g. aortic stenosis, cardiomyopathy, etc):
- ☐ Aneurysmal subarachnoid hemorrhage If yes, days after initial ED evaluation:
- ☐ Major bleed/anemia If yes, days after initial ED evaluation:
  Indicate type of bleed (e.g. GI bleed, ruptured AAA, etc):
- ☐ Major Cardiac Procedure If yes, days after initial ED evaluation:
  Indicate type of procedure (e.g. CABG, valve surgery, pacemaker, etc):
- ☐ Other unusual events noted in discharge summary:
- ☐ Readmission after initial ED evaluation/admission If yes, days after initial ED evaluation:
  Indicate reason for readmission:
- ☐ NONE