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# Utility of Serum S100B Level, SFSR and OESIL Scores in Anticipating Short Term Adverse Events of Discharged Syncope Patients

## Serum S100B Düzeyi ile SFSK ve OESIL Skorlarının Taburcu Edilen Senkop Hastalarının Erken Dönem Advers Olaylarını Öngördürmedeki Değerliliği

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## Abstract

**Objective:** Our aim is to evaluate S100β in serum in addition to clinical syncope decision rules and to determine the utility of this parameter along with OESIL and SFSR for any short term (10 days) adverse events.

**Material and Methods:** This observational prospective cohort study included all consecutive patients older than 18 years who presented to the ED of Marmara University Hospital between June 2005 and January 2007 with the complaint of syncope within the previous 48 hours unless they had exclusion criteria. Two hundred and fifty-four patients were admitted, 80 were enrolled and 62 completed the follow-up. Multivariable logistic regression analysis was used to develop a risk score to predict the probability any adverse event in the short term using parameters of OESIL risk score, SFSR and serum S-100β level.

**Results:** Patients with any short term adverse events had a higher pulse rate, lower hematocrit and hemoglobin levels, and higher serum S100B levels on admission. There were no significant differences between the accuracies of OESIL, SFS Rule and S100B level. Absence of prodromal symptoms, abnormal ECG and high serum S100B level were significant contributors of the model of adverse events. OESIL and S100B level were relatively effective compared to SFSR. The predictive value of each risk score was increased when combined with S100B level.

**Conclusion:** The OESIL and SFSR were ineffective in recognizing patients with adverse events because of relatively low sensitivity. Serum S100B level seems to be a promising biochemical test which may increase the utility of prognostic syncope risk scales. *(JAEM 2013; 12: 1-7)*

**Key words:** S100B protein, syncope, sensitivity and specificity

## Özet

**Amaç:** Serum S100β değerini OESIL ve San Fransisko Senkop Kuralı (SFSK) gibi senkop klinik karar verme kurallarıyla birleştirerek erken dönem (10 gün) advers olay riskini belirlemede sağladığı faydayı belirlemeyi hedefledik.

**Gereç ve Yöntemler:** Bu gözlemsel prospektif kohort çalışmasına, 2005 Haziran ve 2007 Ocak ayları arasında Marmara Üniversitesi Acil Servisine son 48 saat içerisinde bayılma şikayetiyle başvuran, 18 yaşından büyük ve dışlanma kriterlerini içermeyen tüm hastalar dahil edilmiştir. Taranan 254 hastadan 80'i çalışmaya dahil edilmiş, 62'si çalışmayı tamamlamıştır. OESIL ve SFSK'nın parametreleri ve serum S100β değeri çoklu regresyon analizi ile incelenerek erken dönemde herhangi bir advers olay olasılığını öngördürecek bir risk skoru geliştirilmeye çalışılmıştır.

**Bulgular:** Erken dönemde advers olay görülen hastaların başvuru esnasında daha yüksek nabız hızı, daha düşük hematokrit ve hemoglobin düzeyleri ve daha yüksek serum S100β düzeyine sahip oldukları belirlenmiştir. OESIL skoru, SFSK ve S100β düzeylerinin kesinlikleri (accuracy) arasında istaitstiksel olarak anlamlı fark tespit edilmemiştir. Prodromal semptom olmaması, anormal EKG varlığı ve yüksek serum S100β düzeyi advers olayı belirleyebilecek regresyon modeline anlamlı katkıda bulunan değişkenler olarak belirlenmişlerdir. OESIL risk skoru ve S100B düzeyi SFSK ile karşılaştırıldığında nispeten daha etkin gibi görünmektedirler. Öte yandan, her skorun prediktif değeri S100B ile birleştirildiğinde yükselmektedir.

**Sonuç:** OESIL risk skoru ve SFSK erken dönemde advers olay geçirmesi muhtemel hastaları belirlemede düşük duyarlılıkları sebebiyle yeterli değillerdir. Öte yandan, serum S100B düzeyi bu progrnostik risk skorlarının değerliliğini arttıracak bir biyokimyasal test olabilir. *(JAEM 2013; 12: 1-7)*

**Anahtar kelimeler:** S100B proteini, senkop, duyarlılık ve özgüllük

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## Introduction

Syncope is a complex symptom consisting of transient loss of consciousness and loss of postural tone which completely recover within a few minutes (1-5). Although syncope usually results from benign causes and has a good prognosis, the mortality rates are between 6-33% depending on the etiology, and this leads to a high rate of hospital admission. This rate depends on several factors: it is difficult to diagnose the exact etiology of syncope in the emergency department (ED) because of time constrains and unavailable diagnostic tests, cardiac syncope has a high mortality rate of up to 30% and specific protocols to admit or discharge these patients do not exist (6). Lack of diagnostic tests led to the development of new prognostic and diagnostic scores to stratify the risk for these patients. The Osservatorio Epidemiologico sulla Sincope nel Lazio (OESIL) risk score is a prognostic score which was developed from mortality and morbidity rates at 12 months after the syncopal event, and it has been designated to provide accurate guidelines for hospital admission (6, 7). On the other hand, another prognostic score, San Francisco Syncope Rule (SFSR), was based on adverse outcomes within 7 days after the ED evaluation (8). Nevertheless, validification of SFSR has yielded discordant results (9-11).

The glial-derived protein S-100β is an established biochemical marker for demonstrating cerebral injury observed in conditions such as head trauma, cerebral infarct, cardiac arrest and cardiac surgery and it has been proved to be a useful marker of global anoxia. There is a correlation between the severity of ischemic lesions and serum levels of S100B (12). In a recent case report, it is argued that hypoxic syncope in a competitive breath-hold diver may increase levels of S-100β in serum (13). The major pathway leading to syncope is the dysfunction of the reticular activating system and both cerebral hemispheres as a result of hypoperfusion (14-17). So, any type of prolonged syncope leading to cerebral hypoperfusion or hypoxia may increase levels of S-100β in serum, and these patients may have a higher short term adverse event risk compared to patients with brief syncope episodes.

Thus, evaluation of serum S-100β levels in syncope patients may have a valid basis in addition to clinical decision rules and we aimed to determine the utility of this parameter along with OESIL and SFSR for any short term (10 days) adverse event (ie, death, the need for major therapeutic procedures, and early readmission to hospital). This is, to our knowledge, the first study to investigate the value of serum S-100β levels as a marker for syncope.

## Material and Methods

### Study Population

This observational prospective cohort study included all consecutive patients older than 18 years who presented to the ED of Marmara University Hospital between June 2005 and January 2007 with the complaint of syncope within the previous 48 hours.

### Respective Methodology

Symptoms, findings and complaints regarded as a potential syncopal event are as follows: loss of consciousness, presyncope, fainting, collapse, light-headedness, dizziness, falls, seizures, head injury, and bone fractures. The exclusion criteria used to determine the target population were as follows: (i) age <18; (ii) no consent; (iii) the presence of clinical conditions known to increase serum S-100β levels (eg., malignant melanoma, shock state); (iv) confirmed nonsyncopal syndromes such as vertigo, coma, shock, witnessed seizure, sustained unconsciousness, head injury preceding loss of consciousness, stroke; (v) unable or not feasible for follow-up (out of town residents, homeless); (vi) presence of a clinical condition that require admission such as acute myocardial infarction, pulmonary embolism, intracranial hemorrhage, sustained symptomatic bradycardia and tachycardia; (vii) comorbidities with low survival rate.

As shown in Figure 1, 80 patients were enrolled and evaluated according to syncope guidelines (18, 19). Physicians were free to discharge or admit patients according to their clinical decision. OESIL risk score and SFSR score were calculated later from the data collected and a blood sample drawn on admission was reserved for analysis of serum S-100β protein level (20). Physicians at the ED were blind to the patients' serum S-100β levels and physicians at the follow-up were blind to the syncope scores and serum S-100β levels.

Any adverse event includes death, the need for major therapeutic procedures, and early readmission to hospital. An early readmission was defined as any patient discharged from ED after syncope and then readmitted to hospital for the same or similar symptoms in keeping with previous studies (6, 19). These patients were considered to be at high risk for developing a severe outcome. An abnormal electrocardiogram (ECG) was defined as having any of the following in keeping with the criteria used in OESIL risk score and a recent trial (6): (i) atrial fibrillation or tachycardia; (ii) sinus pause of 2 seconds or more; (iii) sinus bradycardia with heart rate ranging between 35 and 45 beats per minute; (iv) any conduction block; (v) signs of previous myocardial infarction or ventricular hypertrophy; (vi) multiple premature ventricular beats. All the ECG's were analyzed by a senior emergency physician during the patient management phase and then by a cardiologist blinded to the risk scores of the patients.

All discharged and admitted patients or their tutors were surveyed on the 10th day of the index event by a follow-up examination or interview and presence of any adverse event was sought.

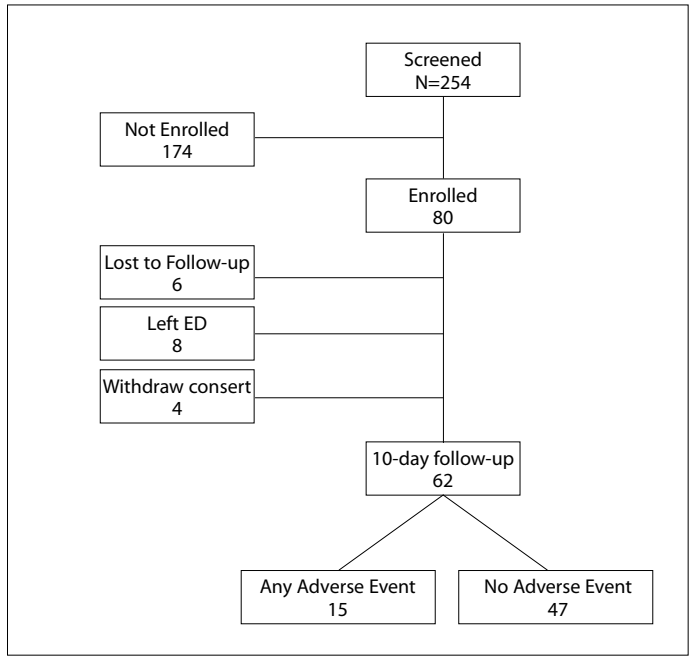


**Figure 1.** Patient flow diagram

Components of the OESIL risk score is as follows: abnormal ECG, a previous history of cardiovascular diseases, absence of prodromal symptoms, and age greater than 65 years. In keeping with the OESIL score, a score of 0 or 1 was considered as low, a score of 2 or more was considered as high risk (7). A patient with any of the following risk factors were considered to be at high-risk according to the SFSR (8): history of congestive heart failure, hematocrit <30%, abnormal ECG, shortness of breath, and systolic blood pressure <90 mm Hg.

On admission, plasma samples were collected and stored at -40°C in tubes containing EDTA until they were analyzed. The day before the analysis, samples were transferred to +4°C. For biochemical analysis CanAg S-100β EIA kit (CanAg Diagnostics AG, Gothenburg, Sweden) was used at room temperature (22°C) according to the manufacturer's label instructions. According to the manufacturer, in a randomly selected population sample of normal volunteers, 20 ng/L has been found to be the cut-off for the 97.5$^{th}$ percentile.

**Statistical Analyses**

We aimed to assess the efficacy of the OESIL risk score, SFSR and serum S-100β levels in recognizing patients with a high risk of any adverse event within 10 days (short-term).

The SPSS version 15 (IBM, New York, USA) was used for descriptive data analysis. All variables are presented as either means with SD or medians with interquartile range (IQRs), as appropriate for the distribution of the data. Categorical variables are presented as percentages with 95% confidence intervals (CIs). Estimates of sensitivity, specificity, and positive and negative likelihood ratios with 95% confidence intervals (CIs) were calculated at each potential decision threshold for OESIL risk score, SFSR and dichotomized S-100β level. The prognostic accuracy of the risk scores was compared by generating receiver operating characteristic (ROC) curves and comparing the area under the curve (AUC) using the method described by Hanley and McNeil for comparing ROC curves derived from the same cases (MedCalc Software version 10.4.0.0; MedCalc, Mariakerke, Belgium). When assessing potential decision thresholds in each respective risk score, our goal was to achieve a near 100% sensitivity to need for intervention or death at the highest possible specificity. We dichotomized these scores as high and low risk values from the decided thresholds. Then, we computed the sensitivity, specificity, positive and negative likelihood ratios, and positive and negative predictive values of each prognostic risk factor.

Multivariable logistic regression analysis was used to model the independent associations' demographic factors, S-100β level and whether any adverse event has happened, while controlling for sex and age as possible confounders. The results of the multivariable logistic regression analysis were used to develop a risk score to predict the probability of any adverse event in the short term using parameters of OESIL risk score, SFSR and serum S-100β level as primary predictors. The relative associations of each variable as represented by their respective regression coefficients were used to derive the risk score. Regression diagnostics were performed, and discrimination was assessed using the area under the ROC curve.

Using a 2-sided $\alpha$ of 5% and a minimum power of 80%, we estimated care requiring 10 cases with adverse events and 40 cases with no complications to detect a difference of 20 ng/L in serum S-100β level. We enrolled 80 patients, but 12 cases had adverse events and 47 cases with no complications have completed the study. The power of the completed study is 81%.

Approval for this study was obtained from the ethical standards committee of Marmara University hospital. Written informed consent was obtained from all patients (or guardians of patients) participating in the study.

## Results

The mean age of the 21 men was 58.24±15.65 (95% CI: 51.11-65.36), and 41 women was 50.10±21.22 years (95% CI:43.40-56.80) in the study population. Demographic and clinical features, components of OESIL and SFSR scores, and serum S100B levels of the study population according to the primary outcome of "any adverse event on the 10th day" are summarized in Table 1. Patients with any adverse events in the short term had a higher pulse rate, lower hematocrit and hemoglobin levels, and higher serum S100B levels on admission.

Dichotomized OESIL and SFSR risk scores (as low/high) were highly correlated with each other (r=0.62; p<0.001), however, their correlation with qualitative S100B level (positive/negative) were low (vs OESIL r=0.24; and vs SFSR r=0.25).

ROC curves of OESIL, SFSR and S100B vs any short term adverse event were drawn (Figure 2) and the accuracy of each score and level were compared as described by Hanley&McNeil (AUC: OESIL 0.78±0.08; 95% CI 0.66 to 0.87; S100B level 0.89±0.06; 95% CI 0.78 to 0.95; SFSR 0.76±0.09; 95% CI 0.63 to 0.86). According to pairwise comparisons, there were no significant differences between the accuracies of each score and S100B level (OESIL vs S100B, p=0.21; OESIL vs SFSR, p=0.79; S100B vs SFSR, p=0.17).

In keeping with the previous research and derivation cohort, an OESIL and SFSR score of 0 was considered to represent low risk, on the other hand, scores of 1, 2 and 3 were assumed to represent high risk for short term readmission. According to the manufacturer, the normal level of S100B was below 20 ng/L. The interval likelihood ratios of each score and level for the prediction of any adverse event were shown in Table 2. Diagnostic utility of each score and test were compared in Table 3.

We created logistic regression models from the components of SFSR and OESIL score, and then we added the S100B level variable to these models to determine whether the serum S100B level signifi-

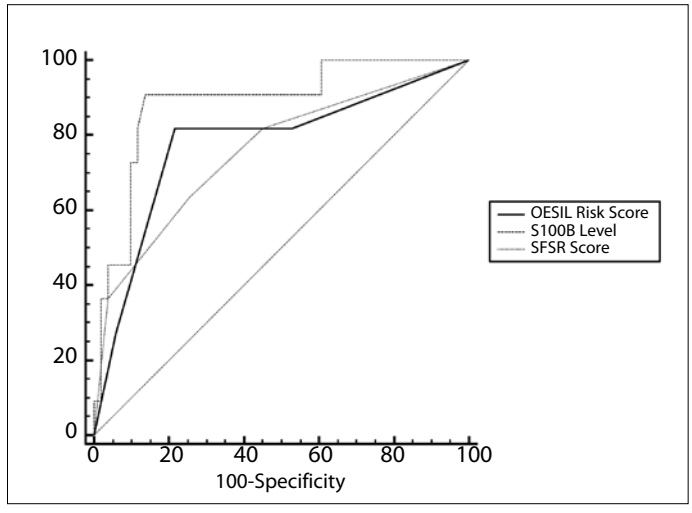


**Figure 2.** Comparison of the ROC curves of S100B levels and OESIL, SFSR risk scores

**Table 1.** Demographic and clinical features of the population studied (n=62)

| **Continuous Variables on admission** | **No Adverse Event** | | **Any Adverse Event** | | |
|---|---|---|---|---|---|
| | **Mean (SD)** | | **Mean (SD)** | | **p value** |
| Age (years) | 50.82 (19.71) | | 62.27 (17.98) | | NS |
| Systolic BP (mmHg) | 113.73 (22.76) | | 125.45 (29.78) | | NS |
| Diastolic BP (mmHg) | 67.55 (15.24) | | 71.82 (16.62) | | NS |
| MAP (mmHg) | 82.94 (16.44) | | 89.70 (20.08) | | NS |
| Pulse rate (/min) | 85.10 (18.16) | | 104.45 (41.90) | | p=0.01 |
| Temperature (C) | 36.5 (0.5) | | 36.5 (0.6) | | NS |
| Hematocrit (%) | 36.9 (5.6) | | 32.7 (7.8) | | p=0.04 |
| Hemoglobin (g/dL) | 12.7 (1.9) | | 11.1 (2.6) | | p=0.02 |
| QTc interval (ms) | 394.39 (21.17) | | 388.09 (19.71) | | NS |
| PR interval (ms) | 161.08 (24.09) | | 163.64 (18.21) | | NS |
| Glucose (mg/dL) | 113.76 (31.84) | | 132.82 (33.35) | | NS |
| S100B Level (ng/L) | 39 (175) | | 361 (694) | | p=0.004 |
| **Categorical Variables on admission** | **n** | **%** | **n** | **%** | **p value** |
| Sex | | | | | |
| Male | 15 | 39.4 | 6 | 54.5 | NS |
| Female | 36 | 70.6 | 5 | 45.5 | |
| Age | | | | | |
| <65 years | 36 | 70.6 | 6 | 54.5 | NS |
| >=65 years | 15 | 29.4 | 5 | 45.5 | |
| History of CAD | | | | | |
| Present | 49 | 96.1 | 10 | 90.9 | NS |
| Absent | 2 | 3.9 | 1 | 9.1 | |
| History of CHF | | | | | |
| Present | 47 | 92.2 | 8 | 72.7 | NS |
| Absent | 4 | 7.8 | 3 | 27.3 | |
| Conduction defect | | | | | |
| Present | 48 | 94.1 | 10 | 90.9 | NS |
| Absent | 3 | 5.9 | 1 | 9.1 | |
| Hypertension | | | | | |
| Present | 30 | 58.8 | 4 | 36.4 | NS |
| Absent | 21 | 41.2 | 7 | 63.6 | |
| Orthostatic hypotension | | | | | |
| Present | 42 | 82.4 | 6 | 54.5 | NS |
| Absent | 9 | 17.6 | 5 | 45.5 | |
| Prodromal symptoms | | | | | |
| Absent | 7 | 13.7 | 6 | 54.5 | p=0.007 |
| Present | 44 | 86.3 | 5 | 45.5 | |
| ECG | | | | | |
| Abnormal | 17 | 33.3 | 9 | 81.8 | p=0.005 |
| Normal | 34 | 66.7 | 2 | 18.2 | |

| | | | | | |
|---|---|---|---|---|---|
| Hematocrit | | | | | |
| <%30 | 6 | 11.8 | 4 | 36.4 | NS |
| >=%30 | 45 | 88.2 | 7 | 63.6 | |
| Dyspnea | | | | | |
| Present | 5 | 90.2 | 3 | 72.7 | NS |
| Absent | 46 | 9.8 | 8 | 27.3 | |
| Hypotension | | | | | |
| <90 mmHg | 6 | 11.8 | 1 | 9.1 | NS |
| >=90 mmHg | 45 | 88.2 | 10 | 90.9 | |
| S100B Level | | | | | |
| <20 ng/L | 41 | 80.4 | 1 | 9.1 | p<0.0001 |
| >=20 ng/L | 10 | 19.6 | 10 | 90.9 | |
| OESIL Risk Score | | | | | |
| Low | 24 | 47.1 | 2 | 18.2 | NS |
| High | 27 | 52.9 | 9 | 81.8 | |
| SFSR Score | | | | | |
| Low | 28 | 54,9 | 2 | 18.2 | p<0.05 |
| High | 23 | 45.1 | 9 | 81.8 | |

BP: Blood Pressure, MAP: Mean Arterial Pressure, CAD: Coronary artery disease, CHF: Congestive Heart Failure, HT: Hypertension, Hct: Hematocrit, ECG: Electrocardiogram, NS: Not significant

**Table 2.** Interval Likelihood Ratios of different OESIL, SFSR Risk Scores and qualitative S100B Levels

| **OESIL Score** | **No Adverse Event n (%)** | **Any Adverse Event n (%)** | **Likelihood Ratio** | **95% CI** |
|---|---|---|---|---|
| 0 | 24 | 2 | 0.386 | 0.106 to 1.084 |
| 1 | 16 | 0 | 0.000 | 0 to 0.858 |
| 2 | 8 | 6 | 3.477 | 1.448 to 7.644 |
| 3 | 3 | 3 | 4.636 | 1.144 to 17.526 |
| SFSR Score | | | | |
| 0 | 28 | 2 | 0.331 | 0.092 to 0.914 |
| 1 | 10 | 2 | 0.927 | 0.927 to 2.959 |
| 2 | 11 | 3 | 1.264 | 1.264 to 3.269 |
| 3 | 2 | 4 | 9.273 | 2.148 to 38.958 |
| S100B Level | | | | |
| <20 ng/L | 41 | 1 | 0.113 | 0.020 to 0.475 |
| >= 20 ng/L | 10 | 10 | 4.636 | 2.550 to 8.412 |

**Table 3.** Comparison of effectiveness of dichotomized OESIL risk score, SFSR and S100B Risk Levels (Low/High Risk) in recognizing patients at high risk for short term adverse events (10 days)

| | **OESIL Risk Score** | | **SFSR Score** | | **S100B Level** | |
|---|---|---|---|---|---|---|
| | **%** | **95% CI** | **%** | **95% CI** | **%** | **95% CI** |
| Sensitivity | 81.8 | 47.8 to 96.8 | 81.8 | 47.8 to 96.8 | 90.9 | 57.1 to 99.5 |
| Specificity | 47.1 | 33.2 to 61.4 | 54.9 | 40.5 to 68.6 | 56.9 | 42.3 to 70.4 |
| Positive Likelihood Ratio | 1.55 | 1.06 to 2.26 | 1.81 | 1.20 to 2.74 | 2.11 | 1.46 to 3.04 |
| Negative Likelihood Ratio | 0.39 | 0.11 to 1.41 | 0.33 | 0.09 to 1.20 | 0.16 | 0.02 to 1.07 |
| Diagnostic Odds ratio | 4 | 0.79 to 20.37 | 5.48 | 1.08 to 27.92 | 13.18 | 1.57 to 110.82 |

cantly increased the predictive power of these scores, or not. The model with the 4 components of OESIL risk score predicted the presence of any adverse event in the short term with the accuracy of 86.9%, could explain 40% of the variance of this outcome (Nagelkerke $R^2$=0.397; Cox&Snell $R^2$=0.234), and the difference between the model and the constant was statistically significant (p=0.003). However, only two components of the OESIL risk score contributed significantly to this model. Wald statistics of "absence of prodromal symptoms" and "abnormal ECG" variables were statistically significant (p=0.047 and p=0.036, respectively), with significant odds ratios (Exp(B)prodromal=5.204 and Exp(B)abnormalECG=10.792). "Age over 65" and "History of CAD" were insignificant contributors. Addition of "S100B level" into OESIL risk score model significantly increased the model's predictive power (p=0.001), accuracy (91.8%) and the explained variance of the outcome (Nagelkerke $R^2$=0.701; Cox&Snell $R^2$=0.414). Even though the model with the 5 components of the SFSR was significant, the only variable that significantly contributed (Wald statistics p=0.047) to the prediction of the outcome was "Abnormal ECG" (Exp(B)abnormalECG=10.180; 95% CI:1.026 to 101.019). Addition of "S100B level" into the SFSR model significantly increased the model's predictive power (p=0.001), accuracy (90.2%) and the explained variance of the outcome (Nagelkerke $R^2$=0.6; Cox&Snell $R^2$=0.354). We also tested another model by including variables which were significantly different between outcome groups, or correlated highly with the outcome of having any adverse event. As reported in Table 1, 5 variables that were eligible and included in this new model are: hemoglobin and hematocrit levels, absence of prodromal symptoms (OESIL component), abnormal ECG (OESIL and SFSR component), pulse rate and S100B levels. In keeping with the previous models, "absence of prodromal symptoms", "Abnormal ECG" and serum S100B level variables were the significant contributors of the model (Nagelkerke $R^2$=0.672; Cox&Snell $R^2$=0.397).

## Discussion

In the ED, emergency physicians are expected to distinguish syncope that will have any major adverse events in the short term period from the low risk ones. Clinical risk scores are proposed to risk stratify these patients and to help in the decision making process (7, 8, 14).

In this study, the level of S100B protein, which is shown to increase as a result of various globally hypoperfusing states (21-23) and after brain injury (24-27), is found to be significantly higher in syncope patients with any adverse event. Patients with any short term adverse events tend to have higher pulse rate, lower hemoglobin and hematocrit levels, have abnormal ECG, no prodromal symptoms and higher serum S100B levels on admission. Any patient with these properties on admission would probably have cardiac or hypovolemic syncope etiologies, which increase their odds to have an adverse event in the short term. Therefore, using these criteria as predictors seems to have a valid basis.

However either the OESIL risk score (7) or the SFSR (8) did not have adequate sensitivity to identify patients that can be safely discharged from ED. In fact, 20% of syncope patients with short term adverse events would have been discharged according to these scores. These figures are compatible with recent findings from different studies (6). Despite the higher sensitivity of serum S100B levels, 9% of syncope patients with adverse events would be missed. The post-test probability of developing a serious adverse event for a patient presenting to ED for syncope would be 2.34%, 1.98% and 0.66%, respectively, for OESIL risk score, SFSR and serum S100B level (28).

To better evaluate these risk scores and serum S100B level relationships, we used a multivariate logistic regression analysis considering the components of risk scores and serum S100B level as predictor and the adverse events as dependent variables. OESIL risk score and S100B level were relatively effective compared to SFSR. On the other hand, the predictive value of each risk score was increased when combined with S100B level.

The OESIL risk score and SFSR had comparable sensitivity and specificity in the short term, although the former was obtained from a 1 year follow-up mortality, on the other hand the SFSR was based on adverse events within 7 days (6). However, these two scales are closely related since their components either directly or indirectly reflect the same abnormalities. Some of these components, such as an abnormal ECG or absence of prodromal symptoms, had significantly higher odds of predicting prognosis compared to other variables. Therefore, S100B may be a useful contribution to these specific risk factors in predicting short term adverse events.

Concordance of OESIL risk score and SFSR was higher in the present study (K=0.71) compared to previous studies (6). Since both scales have cardiac risk factors in common, in a study population with higher proportion of cardiac syncope, this concordance is expected to increase. This may be the cause of elevated S100B levels in adverse event group.

### Limitations

This study has several potential limitations. The most important one is the variation among the arrival time of the patients after the index syncopal event. Unfortunately, patients do not present at the EDs as soon as they have experienced syncope. Thus, blood samples were taken at a time range between 15 minutes to 6 hours after the index event, which might have affected serum S100B levels.

Although we tried to minimize selection and misclassification biases by tight inclusion and exclusion criteria, close oversight of data collection, and independent blinded confirmation of each patient's diagnosis, there is a potential for a small degree of misclassification bias of patients with seizure or conversion disorder as having a syncopal event.

The limitations of the regression models are as follows: Number of patients with any adverse event was low in the study population, which decreased the reliability of these analyses with the increasing number of variables. Also, we had to omit two cases with high Cook's distances and standardized residues from regression analyses since these cases were regarded as outliers. Therefore, the external validity and generalizability of our findings will have to be confirmed in a larger and different cohort of patients. This study was also limited by the relatively small number of included patients.

We did not collect any data from echocardiography, electroencephalography, computed tomography, cardiac stress test, or tilt test and thus we might have missed some valuable information that could be incorporated into regression models. It is unclear how the inclusion of such information might have affected results.

## Conclusion

The OESIL risk score and the SFSR were ineffective in recognizing patients with adverse events in the short term because of a relatively

low sensitivity. On the other hand, serum S100B level seems to be a promising biochemical test which may increase the utility of prognostic syncope risk scales. However, S100B level might be increased in a specific subgroup of syncope patients with a particular etiology which would have a high rate of adverse events. Therefore, identification of subgroups which might have higher S100B levels needs to be evaluated.

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**Conflict of Interest**

No conflict of interest was declared by the authors.

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