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Predictive performances of STESS and EMSE in a Norwegian adult status epilepticus cohort

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ABSTRACT

Purpose: "Status Epilepticus Severity Score" (STESS) and "Epidemiology-based Mortality Score in Status Epilepticus" (EMSE) are two clinical scoring systems aiming to predict mortality in status epilepticus (SE). The objective of this study was to compare their predictive performances in a cohort of 151 SE-patients from Oslo University Hospital in the period 2001–2017.

Method: Variables used to calculate STESS (age, previous seizures, worst SE-semiology, level of consciousness) and two different versions of EMSE, EMSE-EAC (etiology, age, comorbidities) and EMSE-EACE (etiology, age, comorbidities, EEG-pattern), as well as outcome were collected retrospectively. Receiver Operating Characteristic (ROC)-analyses, determination of best cut-off values, sensitivity (Se), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV) were performed. In addition, Precision-Recall curves (PRC) were produced, plotting PPV as a function of Se.

Results: Thirteen patients (9%) died during their hospital stay. STESS did not accurately predict mortality, with a ROC-curve showing an area under the curve (AUC) of 0.625(95%CI = 0.472-0.783), p = 0.15. EMSE-EAC performed better with an AUC of 0.714(95%CI = 0.552-0.873), p = 0.01 and a best cut-off value of 37. Se was 69.2%, Sp 72.1%, PPV 19% and NPV 96.2%. EMSE-EACE performed best with an AUC of 0.855(95%CI = 0.736-0.976), p < 0.0005 and a best cut-off value of 79. Se was 77.8%, Sp 87.8%, PPV 36.8% and NPV 97.7%. The PRC showed areas under the PRC of 0.23 for EMSE-EAC and 0.46 for EMSE-EACE.

Conclusions: EMSE-EAC and EMSE-EACE performed better than STESS and may be useful in identifying the patients at risk of death in SE. PRC may give a more relevant visual representation of predictive utility than ROC-curves in situations of imbalanced datasets.

1. Introduction

Status epilepticus (SE) is a neurological emergency that can sometimes be difficult to treat. Refractory or even superrefractory SE have approximately 3 times higher mortality than the non-refractory forms [1]. Unfortunately, no accurate method of predicting response to treatment and outcome exists. However, over the last years two clinical scoring systems have emerged, designed to predict mortality of SE episodes. Status Epilepticus Severity Scale (STESS) was developed in 2006 by Rossetti et al. [2] and is based on the assessment of four clinical factors at admission (age, level of consciousness, worst clinical seizure type, previous seizures). However, subsequent studies found mixed results for the STESS, with high negative predictive values (NPVs), but low positive predictive values (PPVs) for prediction of death in SE [3–7]. Another scoring system was developed by Leitinger et al. in 2015 [8], Epidemiology based Mortality of Status Epilepticus (EMSE), aiming at producing better PPVs than the STESS. Several versions of EMSE were tested and discussed in the original article, based on different combinations of six clinical factors (age, level of consciousness, etiology, comorbidities, duration of SE and EEG-pattern). The versions of the score that performed the best, with respectively the best PPVs of 44 and 69%, were EMSE-EAC based on etiology, age and comorbidities and EMSE-EACE based on etiology, age, comorbidities and EEG-pattern. Since then, only a few studies have tested the predictive performance of EMSE-EACE and found PPVs varying from 21 to 59.8% [4,6,7].

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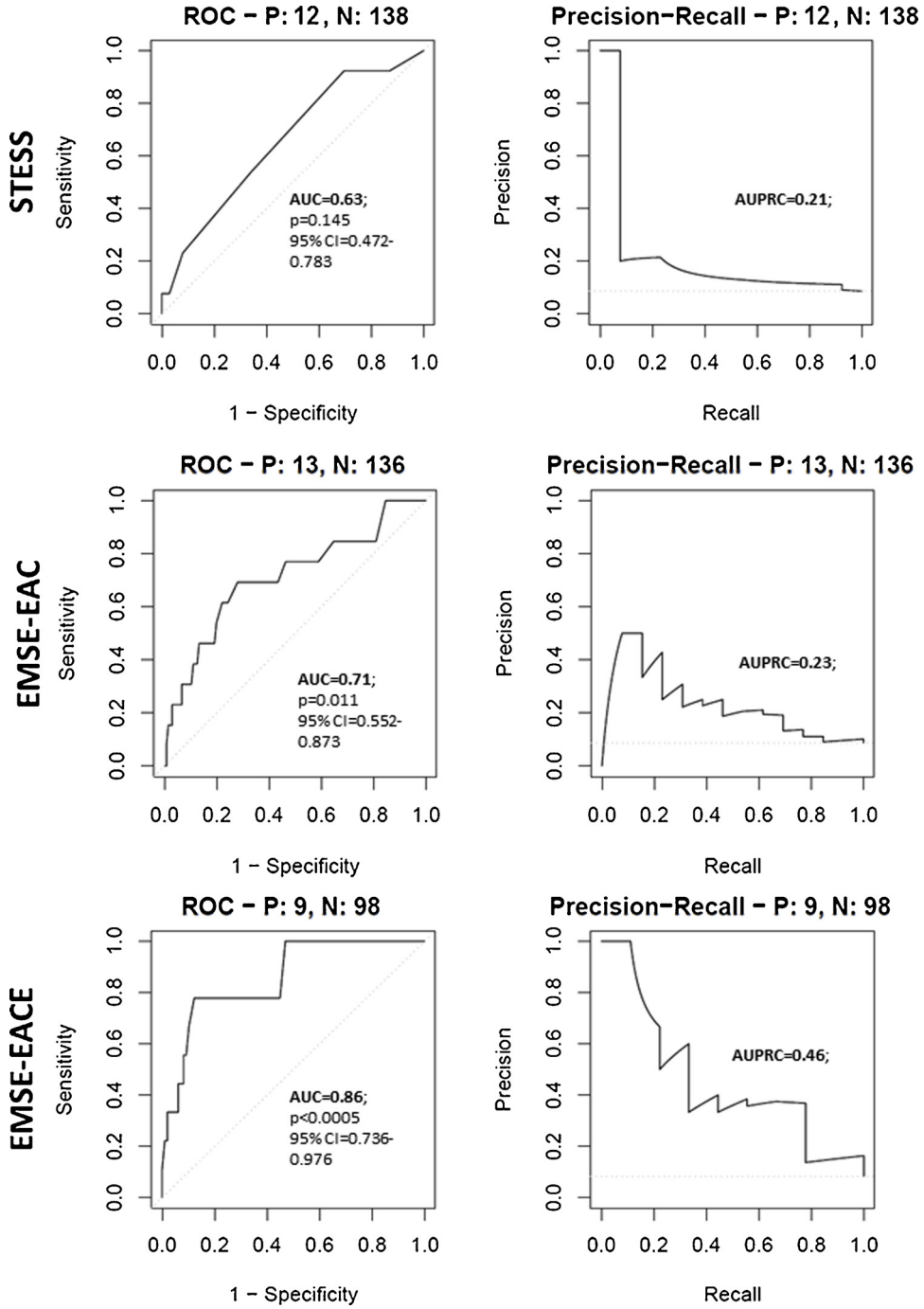

Fig. 1. ROC-curves and PRC for STESS, EMSE-EAC and EMSE-EACE with regard to in-hospital death.
ROC, Receiver Operating Characteristic; PRC, Precision-Recall Curve; STESS, Status Epilepticus Severity Score; EMSE, Epidemiology based Mortality in Status Epilepticus; EAC, Etiology-Age-Comorbidity; EACE, Etiology-Age-Comorbidity-EEG.

The aim of this study was to retrospectively test the predictive performances of STESS, EMSE-EAC and EMSE-EACE in a Norwegian cohort of 151 adult SE-patients, with prediction of in-hospital mortality as primary outcome, and prediction of poor functional outcome and refractoriness as secondary outcomes. In addition to producing the traditional areas under the receiver operating curve (AUROC) for the different scores, we also produced areas under the precision recall curve (AUPRC) [9,10] to give the most relevant possible representation of predictive accuracy and utility. They have recently been described as being more informative than AUROCS in evaluating imbalanced datasets.

2. Methods

2.1. Population and data collection

The SE-cohort was described in detail in a previous article [11]. Data were collected retrospectively by searching in the hospital journal system for neurological/ICU patients with the ICD-10 diagnosis code "status epilepticus" between 2001 and 2017 and entered into a database. SE was defined according to ILAE's latest definition as, for generalized convulsive seizures, seizures lasting at least 5 min or repeated seizures without recovery between the seizures, and for focal seizures, seizures lasting at least 10 min [12]. Variables included in STESS (age,

Table 1
Calibration performances of STESS, EMSE-EAC and EMSE-EACE estimated for different cut-off values using the Expected/Observed (E/O) ratio.

Calibration	STESS		EMSE-EAC		EMSE-EACE	
Cut-off value	≥3	≥4	≥27	≥37	≥64	≥79
Mean observed (O) vs. predicted (E)	9% vs 35%	9% vs 22%	9% vs 46%	9% vs 32%	9% vs 33%	9% vs 18%
E/O	3.9	2.4	5.1	3.6	3.7	2

level of consciousness before treatment, worst clinical seizure type, previous seizures) and in the two different versions of EMSE (age, etiology, comorbidities, EEG-pattern) were assessed retrospectively by minutely going through the patient journals (ambulance officer notes, nurse's notes, medical notes). All available EEGs were reassessed and rescored according to the EMSE scoring system. Variables were scored at the earliest possible time point following admission, with the exception of level of consciousness that was sometimes scored before admission if treatment had been initiated prior to admission. The first available EEG was chosen for scoring, performed on day 1–5 depending on the cases. Then the STESS score and the sum scores of EMSE-EAC and EMSE-EACE were calculated for each patient [2,8]. Outcome was assessed by comparing the modified Rankin scale (mRS) at discharge with the baseline mRS. Poor functional outcome was defined as a worsening of the mRS at hospital discharge or death. Refractory SE was defined as persistence of SE despite first- and second-line antiepileptic drugs (AEDs) with a maximum of 2 second-line AEDs. Superrefractory SE (SRSE) was defined as SE that continues or recurs after 24 h of anesthesia or recurs on the reduction or withdrawal of anesthesia.

2.2. Outcome

The primary outcome variable was defined as in-hospital death, and the secondary outcome variables were defined as a poor functional outcome (worsening of the mRS at discharge or death) and as refractoriness (refractory SE or SRSE).

2.3. Statistics

Statistical analyses were performed using SPSS and R. Discrimination was defined as the ability of STESS and EMSE to differentiate survivors from non-survivors (primary outcome), patients who had good functional outcome from patients who had a poor functional outcome (secondary outcome) and patients that had a refractory SE from patients that had a non-refractory SE (secondary outcome). Receiver operating curves (ROC) were constructed for STESS, EMSE-EAC and EMSE-EACE with calculation of the AUROCs. Missing data were excluded from the analysis. We identified the optimal cutoff point of each score regarding sensitivity and specificity for the prediction of outcomes, and then calculated sensitivity, specificity, PPV and NPV for each score. Calibration was evaluated using the Expected/Observed ratio for different cut-off values for STESS, EMSE-EAC and EMSE-EACE. Finally, precision-recall curves (PRC) were constructed using the precrec package in R, and AUPRCs were calculated for STESS, EMSE-EAC and EMSE-EACE with regard to the primary outcome. The dataset with scores and outcome for the 151 patients can be accessed in Mendeley data [13].

3. Results

3.1. Performances of STESS and EMSE in predicting in-hospital death

Overall, 9% (n = 13) of the 151 patients died at the hospital during their SE-episode. Of these, 12 were refractory or superrefractory SE-episodes, and 1 was a responsive SE-episode. Based on the ROCs, STESS did not perform well in the prediction of in-hospital death, EMSE-EAC performed significantly better (fair accuracy, AUROC between 0.7-0.8, p = 0.01) and EMSE-EACE showed the best predictive performance (good accuracy, AUROC between 0.8-0.9, p < 0.001) (Fig. 1).

For EMSE-EAC, the best cut-off value was 37 providing a sensitivity of 69.2%, a specificity of 72.1%, a PPV of 19% and a NPV of 96.2%. The percentage of correctly classified patients was 718% (107/149). For EMSE-EACE, the best cut-off value was 79 providing a sensitivity of 77.8%, a specificity of 87.8%, a PPV of 36.8% and a NPV of 97.7%. The percentage of correctly classified patients was 869% (93/107).

Using the cut-off values of the initial article by Leitinger et al. [8], EMSE-EAC-27 provided a sensitivity of 69.2%, a specificity of 56.6%, a PPV of 13.2% and a NPV of 95.2%, and EMSE-EACE-64 a sensitivity of 77.8%, a specificity of 71.4%, a PPV of 20% and a NPV of 97.2%.

Details regarding calibration can be found in Table 1.

However, considering that death was a rare event which only occurred in 9% of cases, the dataset may be considered imbalanced. To better evaluate the predictive performance, precision-recall curves were therefore constructed and AUPRCs were calculated (Fig. 1). Compared with the AUROCs, AUPRCs were lower for all three scores, pointing towards a lower actual predictive utility than what is suggested by the AUROCs.

3.2. Performances of STESS and EMSE in predicting a poor functional outcome at discharge

Of the 151 patients, 48% (n = 72) had a worsening of their mRS at discharge compared to before the SE-episode, while 52% (n = 79) returned to their baseline mRS.

Based on the ROCs, only EMSE-EACE showed some performance in the prediction of poor functional outcome, but the accuracy is

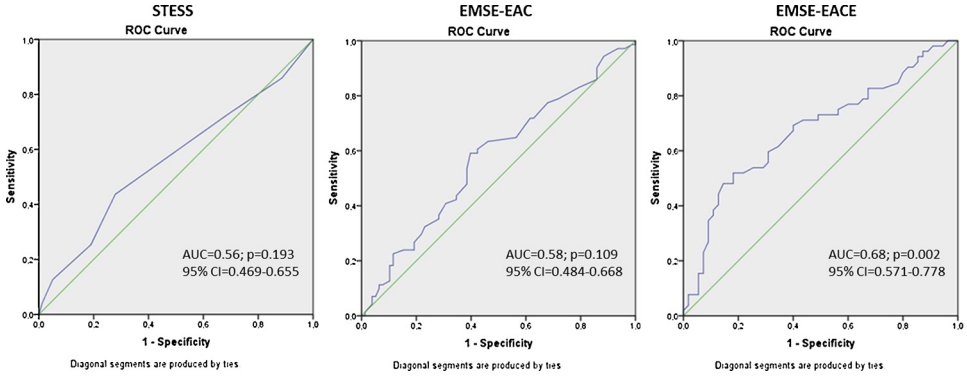

Fig. 2. ROC-curves for STESS, EMSE-EAC and EMSE-EACE in prediction of poor functional outcome.
ROC, Receiver Operating Characteristic; STESS, Status Epilepticus Severity Score; EMSE, Epidemiology based Mortality in Status Epilepticus; EAC, Etiology-Age-Comorbidity; EACE, Etiology-Age-Comorbidity-EEG.

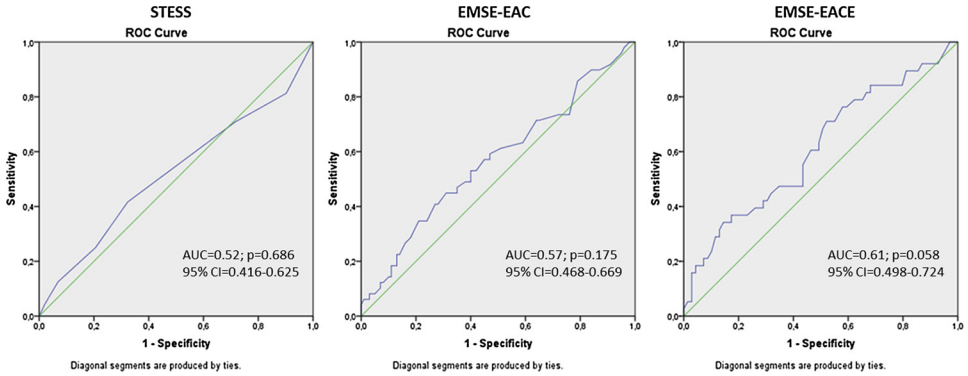

Fig. 3. ROC-curves for STESS, EMSE-EAC and EMSE-EACE in prediction of refractoriness.
ROC, Receiver Operating Characteristic; STESS, Status Epilepticus Severity Score; EMSE, Epidemiology based Mortality in Status Epilepticus; EAC, Etiology-Age-Comorbidity; EACE, Etiology-Age-Comorbidity-EEG.

considered poor with an AUROC between 0.6-0.7 (Fig. 2). The best cut-off value was 61, with a sensitivity of 519%, a specificity of 818%, a PPV of 73% and a NPV of 643%. The percentage of correctly classified patients was 673% (72/107).

3.3. Performances of STESS and EMSE in prediction of refractoriness

Of the 151 patients, 68% (n = 102) had a non-refractory SE, while 32% (n = 49) had a refractory SE (including the SRSE). Neither STESS nor EMSE showed any significant performance in the prediction of refractoriness (Fig. 3).

4. Discussion

STESS and EMSE are new clinical scoring systems aiming at predicting outcome in status epilepticus that could become useful tools for the neurologist in the emergency department and in the intensive care unit if they prove to be informative enough.

4.1. Prediction of in-hospital mortality

In this study, we found that with regard to our primary outcome, in-hospital death after SE, EMSE performed significantly better than STESS. STESS showed a poor predictive discriminative performance that did not reach significance. Of the two versions of EMSE evaluated in our study, EMSE-EAC and EMSE-EACE, EMSE-EACE showed the best predictive discriminative performance with an AUROC of 0.86 which is considered a good accuracy, providing a Se of 778%, a Sp of 878%, a NPV of 97.7% and a PPV of 36.8% using a cut-off value of 79. While the study of Kang et al. [4] did not find a significant difference between STESS and EMSE, our results support the superiority of EMSE to STESS in the prediction of mortality, as did the initial study by Leitinger et al. [8] and a subsequent prospective study by Giovannini et al. [7]. A recent study by Semmlack et al. on 184 SE-patients found that STESS only had limited measures of discrimination for outcome prediction in SE [14].

For both STESS and EMSE, previous studies have found quite low PPVs, ranging from 22 to 45.5% for the STESS [3–7,15], and from 21 to 59.8% for the EMSE-EACE [4,6,7]. However, NPVs have been high, ranging from 74.7 to 100% for the STESS [3–7,15], and from 95.7 to 98% for EMSE-EACE [4,6,7], making the authors conclude that the scores are more useful in predicting survival rather than death. However, considering that death is in fact a rare outcome in SE, this is not a surprising result. Because death is such a rare event it will be hard for even a good model to achieve a high PPV [16]. While PPV and NPV offer the advantage of making individual diagnoses by indicating the probabilities of the outcomes given the classification of a test, they also have the disadvantage of depending on the overall frequency of the considered event in the population. As an example, a standard EEG as a diagnostic test for epilepsy can be considered to have a sensitivity up to 55% and a specificity over 90% [17,18]. If an EEG is performed in an epilepsy monitoring unit where the prevalence of epilepsy is around 75%, the test will produce a PPV of 94%. In this case, the test can be considered to perform well, where a person with a positive test has a 94% probability of having epilepsy. However, if an EEG is performed in the general population where the prevalence of epilepsy is around 1%, the PPV will be 5%, meaning that a person with a positive EEG only has a 5% chance of having epilepsy and the test will be considered poor [19]. A characteristic of prediction models aiming at predicting rare events is that, unless the classifier is perfect, they will produce higher NPVs than the PPVs. In our study, a PPV of 36.8% reflects a 36.8% probability of death given a positive test result using EMSE-EACE. Although the score does not reliably predict death, it may still be useful in identifying SE patients that are particularly at risk.

4.2. Usefulness of Prediction recall curves in identifying patients at risk

Traditional ROC-curves plot sensitivity as a function of (1-Specificity), with the AUROC reflecting the overall discriminative accuracy of the test. The overall discriminative accuracy depends on the accuracy of events (sensitivity) and the accuracy of non-events (specificity). In situations where the frequency of non-events overwhelms the frequency of events, this means that the AUROC will be more driven by specificity than sensitivity, and that reducing the number of false positives will improve accuracy more than reducing the number of false negatives. However, favoring specificity may not always be the most relevant choice with regard to the clinical need, in which case AUROCs may generate excessively optimistic estimates of discriminative utility. Prediction of mortality in status epilepticus patients may be one of these situations where specificity is not the most relevant measure, especially if what we really want is to identify the patients at risk of death rather than the patients that are actually going to die. Because of its low prevalence, perfect prospective discrimination of death will be difficult to achieve. Rather than assuming predetermination, the identification of patients at risk of death could allow for interventions that could change the odds in favor of the patient. In this setting it will be more important to reduce the number of false negatives rather than the number of false positives, to avoid missing patients at risk. It will also be important, for the identified patients, to have a measured estimate of their potential risk. This is provided by the PPV. Because of these considerations, precision-recall curves, that plot PPV as a function of sensitivity, have recently been described as better suited than ROC-curves to evaluate tests that aim at predicting patients at risk for rare events and may at least serve as an interesting complement [10]. In our case, the precision-recall curve for EMSE-EACE gives a realistic and easy-to-interpret visual representation of its predictive utility, with an

easily identifiable best cut-off point of 79 producing a PPV of 368% and a sensitivity of 778%. We calculated the area under the precision-recall characteristic (AUPRC) which is less influenced by nonevents accuracy than AUROCs, and obtained the highest value 0.46 for EMSE-EACE.

4.3. Prediction of poor functional outcome at discharge and prediction of refractoriness

With regard to our secondary outcomes, prediction of poor functional outcome at hospital discharge and prediction of refractoriness, only EMSE-EACE showed a significant discriminative performance in the prediction of poor functional outcome. None of the tests showed any significant performance in the prediction of refractoriness. In a previous study, we showed that EMSE-EACE was associated with poor functional outcome, but predictive performance was not evaluated [11]. Here, the discriminative performance of EMSE-EACE in the prediction of poor functional outcome was evaluated as poor with an AUROC between 0.6 and 0.7, which differs slightly from the results of Giovannini et al. [7] who found a good discriminative performance with an AUROC of 0.80, as well as the results of Kang et al. [4] and Ciurans et al. [20] who found AUROCs > 0.7. The finding that EMSE-EACE may be useful in predicting poor functional outcome and significantly better than STESS is supported by several studies [4,7,20]. Semmlack et al. [14] compared STESS with other illness severity scoring systems and found that STESS showed the best discrimination for a poor functional outcome, but EMSE was not among the tested scoring systems.

Only a few studies have looked at the diagnostic performances of STESS and EMSE with regard to refractoriness [7,21]. It is somewhat surprisingly that none of them have found them to perform well in this regard, because many of the factors that have been found to be associated with refractoriness have also been found to be associated with outcome and have been integrated to the STESS and EMSE scores. However, our study supports that STESS and EMSE do not seem clinically useful in the prediction of refractoriness.

4.4. How EEG increases the predictive performance of EMSE

Interestingly, inclusion of EEG patterns categorized as ictal or periodic into the score increased the diagnostic performance of EMSE with regard to the prediction of outcome, both the in-hospital mortality and poor functional outcome at discharge. Especially periodic patterns have been associated with poor outcome in previous studies. The significance of these patterns is controversial. They are most often considered as patterns belonging to the ictal-interictal continuum, but also as markers of cortical damage [22]. Both hypotheses, the first through a reflection of refractoriness, the second through a reflection of cortical damage, are plausible explanations to the association of these patterns with poor outcome.

4.5. Limitations

The main limitation of our study, like all the above mentioned similar studies, is the low effective sample size especially regarding the number of events for the primary outcome (death). Another limitation is the retrospective character of our study. The scoring of some items like level of consciousness before treatment and worst seizure semiology was based on paramedical and medical notes in the patient's journals, sometimes with some level of uncertainty depending on the quality of the notes. This could have affected the predictive performance of STESS.

Finally, an important limitation is that STESS and EMSE can only be compared on unequal premises. While STESS was designed to be scored on admission, EMSE relies on the scoring on items like etiology and EEG which are often not available at that same time-point. It is unclear when the different items of EMSE should be scored and for which stages of status epilepticus it can be clinically useful. STESS has the advantage of being bedside practical and can be rapidly assessed upon admission. It should be mentioned that a modified version of STESS (mSTESS) was proposed by Gonzalez-Cuevas et al in 2016 [23], which included the assessment of the patient's baseline modified Rankin scale. This score showed better prediction of mortality than STESS, while remaining easily assessable early in the time course of the status epilepticus. A comparison of EMSE with the mSTESS could be interesting for future studies.

In conclusion, the study supports the superiority of EMSE over STESS with regard to prediction of in-hospital mortality and poor functional outcome related to SE, and that especially EEG increases its predictive performance. Although PPVs remain too low to reliably predict death and poor functional outcome, the scores may be useful in identifying those patients that are particularly at risk. When the goal is to identify patients at risk for rare events, Precision-recall curves may give the most relevant representation of predictive utility. However, there is a need for larger studies with greater effective sample sizes, and in order to have an impact the scores should be presented in a clinically practical way.

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