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# Role of comorbidities in outcome prediction after status epilepticus

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1 Table

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**Abstract**

Status epilepticus (SE) is related to significant mortality and morbidity. A reliable prognosis may help better managing medical resources and treatment strategies. We examined the role of preexisting comorbidities on the outcome of SE patients, an aspect that has received little attention to date. We prospectively studied incident SE episodes in 280 adults occurring over 55 months in our tertiary care hospital, excluding patients with post-anoxic encephalopathy. Different models predicting mortality and return to clinical baseline at hospital discharge were compared, which included demographics, SE etiology, a validated clinical SE severity score, and comorbidities (assessed with the Charlson Comorbidity Index) as independent variables. The overall short-term mortality was 14%, and only half of patients returned to their clinical baseline. On bivariate analyses, age, SE severity score, potentially fatal etiologies, and number of pre-existing comorbidities were all significant predictors of both mortality and return to clinical baseline. As compared to the simplest predictive model (including demographics and deadly etiology), adding SE severity and comorbidities resulted in an improved predictive performance (C-statistics 0.84 vs. 0.77 for mortality, and 0.86 vs 0.82. for return to clinical baseline); comorbidities, however, were not independently related to outcome. Considering comorbidities and clinical presentation, in addition to age and etiology, slightly improves the prediction of SE outcome, regarding both survival and functional status. This analysis also emphasizes the robust predictive role of etiology and age.

Status epilepticus (SE) represents a severe medical condition (Neligan & Shorvon, 2011); some independent predictors of dismal outcome have been identified, such as acute or potentially fatal etiology, advanced age, de novo presentation, and consciousness impairment before treatment (Towne et al., 1994; Logroscino et al., 1997; Rossetti et al., 2006). However, these variables encompass only a limited aspect of the clinical background. In fact, the role of previously existing medical problems has received far less attention.

We undertook this analysis, in order to investigate how comorbidities influence SE outcome in addition to other known predictors.

**Methods**

Patients and procedures

We analyzed a prospective registry including all adult patients (16 years and older) with SE admitted to our tertiary hospital between April 1st 2006 and October 31st 2010 (55 months). Details may be found elsewhere (Novy et al., 2010). Briefly, SE was defined as the continuous occurrence of seizures for more than 30 minutes (until 2008), and 5 minutes (since 2008), as suggested by the operational definition (Lowenstein et al., 1999). Seizures were diagnosed clinically, but EEG confirmation (at least 20 minutes recordings with background reactivity evaluation) was required for non-convulsive events. SE episodes were identified by the neurological consultants at our emergency and intensive care units, and by the EEG medical staff. Subjects with post-anoxic SE were not recorded. Only incident cases were considered, to allow to every SE episode an equal chance to reach all possible outcomes. This study was approved by our Ethic Commission.

Variables

Demographics, history of previous seizures, worst seizures type, level of consciousness before treatment, pharmacological treatments and SE etiology were recorded prospectively. The STESS score, a validated SE clinical severity score, including age, history of previous seizures, seizure type

and consciousness was calculated (0-6 points) (Rossetti et al., 2008a) (table 1 in supplementary material) and categorized in ≥ 3 (bad outcome prediction) versus < 3 (good outcome prediction). Etiology was considered "potentially fatal" if potentially leading to death if not specifically treated, as previously described (Rossetti et al., 2006).

The Charlson Comorbidity Index (CCI), a validated score of 19 different medical conditions (table 2 in supplementary material), was used to assess the comorbidities (Charlson et al., 1987). CCI was calculated after discharge, based on the medical files, by identification of all comorbid conditions present on admission (except SE etiology). The CCI was categorized in three groups: CCI=0, CCI=1-2, and CCI ≥3; we also analyzed every medical condition as an individual variable. The clinical condition at hospital discharge represented the primary outcome; it was prospectively collected and categorized into return to clinical baseline (premorbid functional and neurological status), new handicap, or death.

Statistical analyses

Potential predictors were analyzed for their relationship with the outcomes "return to baseline" and "mortality" using $\chi^2$ tests. Stepwise logistic regressions were performed to generate predictive models using potential predictors, including demographics, SE severity, etiology and comorbidities. Age was dichotomized at 65 years; of note, since the STESS includes age, the latter was omitted in models considering this score. Discrimination power was assessed using the C-statistics and 95% confidence intervals, and goodness of fit with the Hosmer-Lemeshow $\chi^2$ test; the AIC and BIC values were used as a rough comparison of the models among them, while formal comparisons among ROC were performed using a non-parametric approach. For multiple comparisons, we conservatively applied Bonferroni corrections to obtain a global P<0.05. Analyses were performed with version 9 of the Stata software (College Station, TX).

**Results**

Among 335 SE events recorded during the study period, we indentified 280 incident episodes. Demographics and most relevant clinical variables of the cohort are illustrated in **Table 1**. Twenty (7%) episodes lasted between 5-29 minutes. Gender was evenly distributed, the mean age was 59.3 (± 18.5) years, and 59% of patients had a *de novo* SE episode. Slightly more than half of the subjects displayed a severely impaired consciousness (only 2.5% had a nonconvulsive status epilepticus in coma), or potentially fatal SE etiologies. Among the most frequent causes, 13.9% of SE were symptomatic of primary brain tumor or meningioma, 12.9% had a central nervous system hemorrhage, 9.7% were symptomatic of an old stroke; 9.6% had a cryptogenic SE. In 55.4% of patients a severe SE was retained (STESS ≥ 3); 10.7% of patients received coma induction for SE treatment. About one third of patients did not have any prior comorbidity, while one third had a moderate, and the last third presented a high comorbidity index.

The overall short-term mortality was 14%, and only half of patients returned to baseline conditions at hospital discharge. In bivariate analyses, age, STESS scores, potentially fatal etiologies, and an increased number of comorbidities were significant predictors of both outcomes, while gender was not (for more details, see table 3 in supplementary material).

Considering in-hospital mortality, all models' calibrations were acceptable and are illustrated in **Figure 1A**; the comparison of the 6 models did not show any significant difference (p=0.1325, $\chi^2$) (for more details about model's calibration, see table 4A in supplementary material). Pairwise analyses were performed using p<0.017 (0.05/3) as a significant threshold. Compared to the simplest model (Model 0), the model including the STESS (Model 1, p=0.166, $\chi^2$) and the best model including CCI (Model 3, p=0.064, $\chi^2$) were not statistically different. The model including both STESS and CCI was better (Model 5, p=0.0158, $\chi^2$), showing a slight improvement of the ROC area (0.77 versus 0.84).

We used a similar approach for return to baseline clinical condition (**Figure 1B**). All models' calibrations were acceptable, except for Model 15 (for more details about model's calibration, see table 4B in supplementary material). The comparison of the 6 models indicated some heterogeneity (p=0.0403, $\chi^2$). The best model, including CCI (model 13), was better than the simplest model (Model 00, p=0.0043, $\chi^2$), corresponding to a modest improvement of the ROC area (0.82 versus 0.86).

To summarize, the best predictive models included: etiology, STESS and each variable of the CCI for mortality (Model 5), and demographics, etiology and each variable of the CCI for return to clinical baseline conditions (Model 13).

**Discussion**

This study shows that medical comorbidities increase relatively marginally the prediction accuracy of SE outcome, and confirms that age and etiology are robust outcome prognosticators in this setting.

Our results are in line with those of previous studies performed on different cohorts (Towne et al., 1994; Logroscino et al., 1997; Rossetti et al., 2006) that identified age and SE etiology as the main independent outcome predictors. In addition, one recent work suggested that patients with a higher number of comorbid conditions have a worse outcome (Koubeissi & Alshekhlee, 2007). However, this large data-based study, focused on convulsive SE, has important limitations: its design included a retrospective identification of subjects with SE and their comorbidities assessment was based on ICD diagnoses (Rossetti et al., 2008b). Moreover the short-term mortality of 3% seems unusually low in this clinical setting, and concomitant medical diagnoses were only identified as independent prognostic factors, without any specific analysis addressing their added value in prognostic models including other major predictors.

Regarding etiology, as SE is often one of the clinical manifestations of brain injury, it seems logical that the nature of that injury will markedly influence prognosis. A massive and irreversible damage predicts *per se* a devastating outcome, whereas reversible conditions such as anticonvulsant drug withdrawal may herald a more favorable outcome after SE. As previously outlined (Rossetti et al., 2006; Novy et al., 2010), "acute etiologies" are less robust in predicting outcome than "potentially fatal" etiologies; this may be related to the fact that the latter encompass those acute and progressive symptomatic etiologies that are more dangerous for the patient.

Our study is limited to a hospital-based cohort, but since SE represents a condition that is predominantly treated at hospitals, this aspect should not affect our results. The second limitation lies in the fact that we only investigated the effect of comorbidities on prognosis at hospital discharge, but we cannot exclude that long-term prognosis may be influenced by comorbidities. The strength of our study builds on its prospective design, and the use of clearly defined inclusion criteria. Our mortality rate (14%), which is in the middle range of population-based assessments in Europe and the US over the last two decades: 7% (Coeytaux et al., 2000) and 22% (DeLorenzo et al., 1996), corroborates our findings. Finally, any score may not reflect exactly the clinical background of a patient, but because the CCI is widely used and validated, it seems to be a reasonable choice to represent patient's comorbidities.

In conclusion, comorbidities and the clinical presentation seem to affect the outcome of SE in a relatively marginal way, while age and etiology appear as robust and widely applicable predictors. This emphasizes the importance of a thorough search for the underlying cause of SE in the clinical setting. Moreover, because the presence of comorbidities does not necessarily predict a bad outcome, this should not dissuade physicians from treating patients with SE and comorbid conditions appropriately. Obviously, comorbidities are important regarding contraindications and side effects of anti-epileptic drugs. In this regard they may influence the outcome by influencing the utilization of specific treatments.

**Acknowledgment**

**Disclosure**

Vincent Alvarez, Jean-Marie Januel and Bernard Burnand have nothing to disclose.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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**Tables & Figures**:

**Table 1**: Tertiary care hospital SE patients' demographics and clinical characteristics

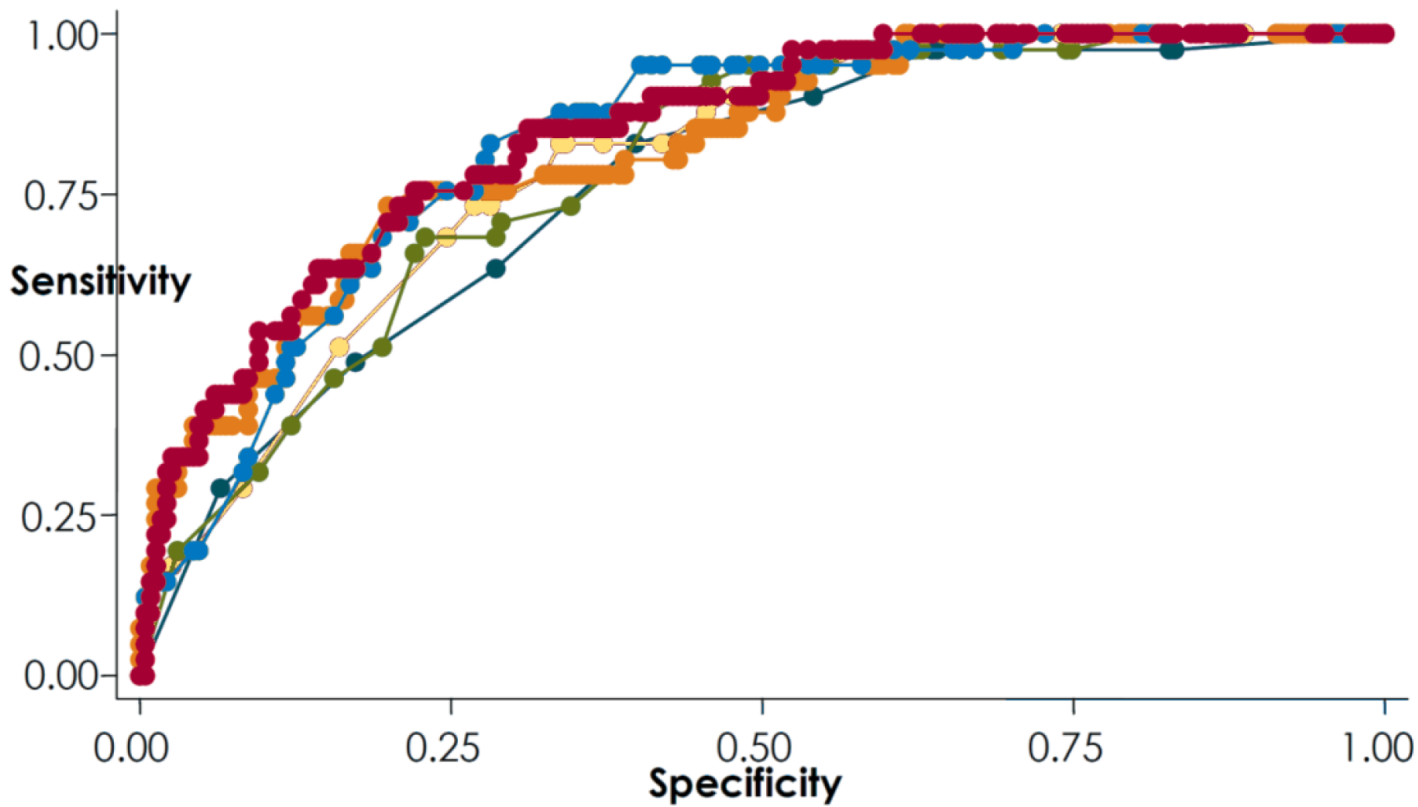| Demographic Data | Number (proportion) |
|---|---|
| | |
| **Gender (Male)** | 139 (49.6%) |
| **Age (SD)** | 59.3 (18.5) |
| **Presence of previous seizures** | 115 (41%) |
| **Severe conscious impairment (stuporous or comatous) before treatment** | 159 (56%) |
| **Deadly etiology** | 129 (46%) |
| **STESS ≥3** | 155 (55.4%) |
| **Coma induction for SE treatment** | 30 (10.7%) |
| **Charlson Comorbidity Score** | |
| 1 | 75 (26.8%) |
| 2 or 3 | 100 (35.7%) |
| ≥3 | 105 (35.5%) |
| **Comorbidities** (according to Charlson et al., 1987) | |
| Cerebrovascular disease | 61 (21.8%) |
| Any tumor | 58 (20.7%) |
| Chronic pulmonary disease | 31 (11%) |
| Solid metastatic tumor | 31 (11%) |
| Congestive heart disease | 25 (8.9%) |
| Moderate/severe renal disease | 23 (8.2%) |
| Dementia | 22 (7.9%) |
| Myocardial infarction | 21 (7.5%) |
| Peptic ulcer | 21 (7.5%) |
| Peripheral vascular disease | 18 (6.4%) |
| Hemiplegia | 16 (5.7%) |
| Moderate /severe liver disease | 14 (5%) |
| Mild liver disease | 11 (3.9%) |
| Diabetes | 9 (3.2%) |
| HIV | 6 (2.1%) |
| Connective tissue disease | 4 (1.4%) |
| Lymphoma | 4 (1.4%) |
| Diabetes with organ damage | 2 (0.7%) |
| Leukemia | 2 (0.7%) |

**Figure 1:** Comparison of 6 predictive models (with model's construction)

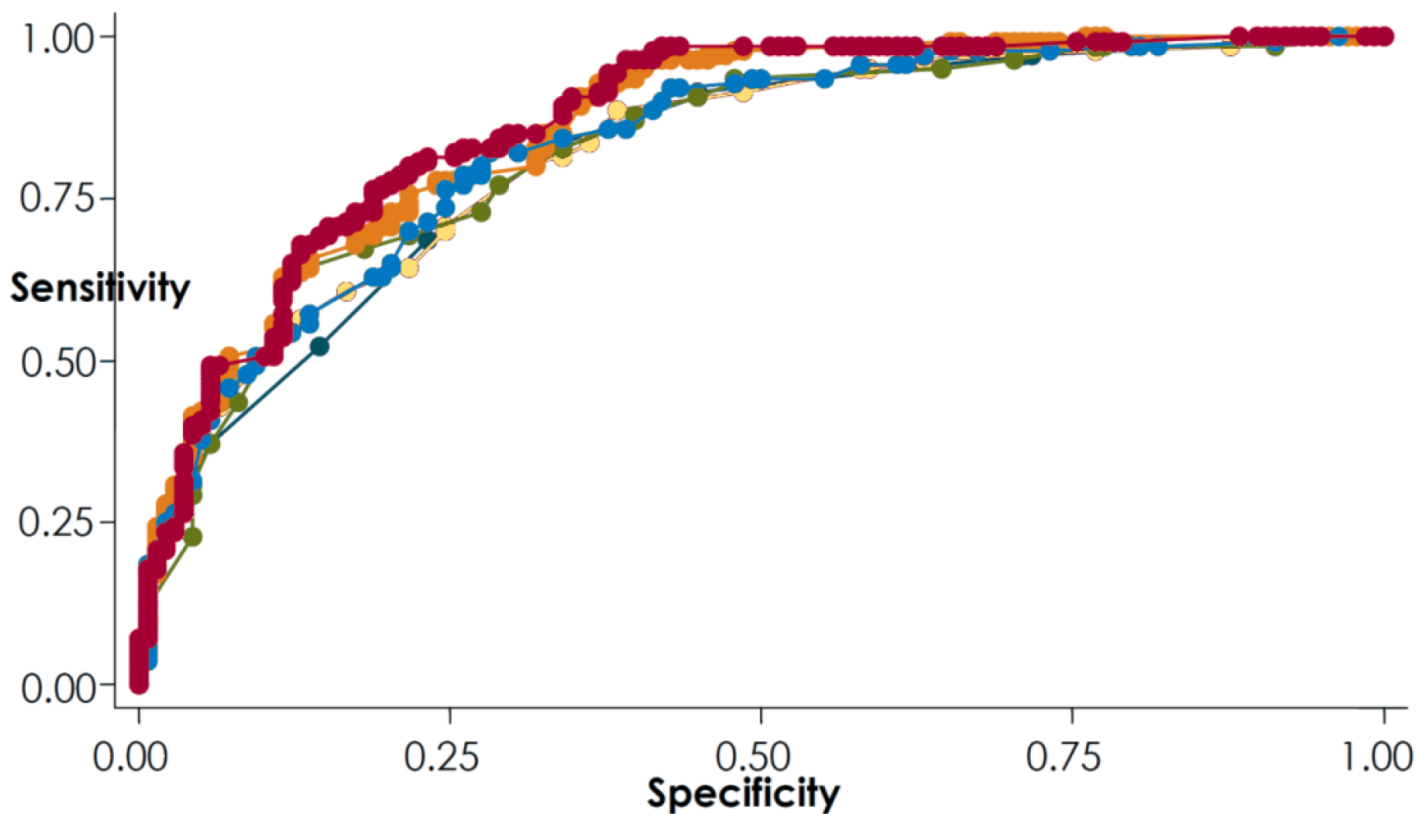**A:** for the outcome "mortality":

- *Model 0* : Gender, age, potentially fatal etiology
- *Model 1* : Gender, potentially fatal etiology, STESS
- *Model 2* : Gender, age, potentially fatal etiology, categorized CCI
- *Model 3* : Gender, age, potentially fatal etiology, each variable of CCI
- *Model 4* : Gender, potentially fatal etiology, STESS, categorized CCI
- *Model 5* : Gender, potentially fatal etiology, STESS, each variable of CCI

**B:** for the outcome "Return to base line":

- *Model 00 :* Gender, age, potentially fatal etiology
- *Model 11 :* Gender, potentially fatal etiology, STESS
- *Model 12* : Gender, age, potentially fatal etiology, categorized CCI
- *Model 13 :* Gender, age, potentially fatal etiology, each variable of CCI
- *Model 14 :* Gender, potentially fatal etiology, STESS, categorized CCI
- *Model 15 :* Gender, potentially fatal etiology, STESS, each variable of CCI

A

mod0 ROC area: 0.76    mod1 ROC area: 0.79
mod2 ROC area: 0.81    mod3 ROC area: 0.82
mod4 ROC area: 0.83    mod5 ROC area: 0.84

B

mod00 ROC area: 0.82    mod11 ROC area: 0.82
mod12 ROC area: 0.83    mod13 ROC area: 0.86
mod14 ROC area: 0.83    mod15 ROC area: 0.86