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**Status epilepticus: impact of therapeutic coma on outcome** CCMED-D-14-01225

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**Abstract**

*Objectives:* Therapeutic coma (TC) is advocated in guidelines for management of refractory status epilepticus (SE); this is however based on weak evidence. We here address the specific impact of TC on SE outcome.

*Design:* Retrospective assessment of a prospectively collected cohort.

*Setting:* Academic hospital.

*Patients:* Consecutive adults with incident SE lasting  $\geq 30$  min, admitted between 2006 and 2013.

*Measurements and main results:* We recorded prospectively demographics, clinical SE features, treatment and outcome at discharge, and retrospectively medical comorbidities, hospital stay, and infectious complications. Associations between potential predictors and clinical outcome were analyzed using multinomial logistic regressions. Of 467 patients with incident SE, 238 returned to baseline (51.1%), 162 had new disability (34.6%), and 67 died (14.3%); 50 subjects (10.7%) were managed with TC. TC was associated with poorer outcome in the whole cohort (relative risk ratio for new disability: 6.86, 95% CI: 2.84-16.56; for mortality: 9.10, 95% CI: 3.17-26.16); the effect was more important in patients with complex partial, compared to generalized-convulsive or nonconvulsive SE in coma. Incidence of infections was higher (OR 3.81, 95% CI: 1.66-8.75) and median hospital stay in patients discharged alive was longer (16 days [range 2-240] vs. 9 days [range 1-57],  $p < 0.001$ ) in subjects managed with TC.

*Conclusions:* This study provides Class III evidence that TC is associated with poorer outcome after SE; furthermore, it portends higher infection rates and longer hospitalizations. These data suggest caution in the straightforward use of this approach, especially in patients with complex partial SE.

## Introduction

Status epilepticus (SE) is the second most frequent neurological emergency after stroke, with an important risk of morbidity and mortality [1-3]. Treatment recommendations for SE are based on a three-step approach [4, 5]; in this context, SE not responding to benzodiazepines (first-line therapy) followed by an antiepileptic drug (second-line therapy) is commonly labeled as refractory SE (RSE). This condition occurs in 23% to 43% of patients with SE [6, 7], and management with therapeutic coma (TC) is advocated in current guidelines (third-line therapy) [4, 5, 8, 9], although there is no high-level evidence.

The effective impact of third-line therapy on outcome, however, has not been clearly established. Recently, a cohort study of 126 patients with SE suggested that this approach may be associated with poorer outcome and death [10], but this analysis was not adjusted for all known principal outcome predictors. Another study including 54 subjects with RSE showed that longer duration of TC is associated with unfavorable prognosis [11]; however, this cohort was restricted to a neurologic intensive care unit (ICU) environment and the authors did not adjust for SE outcome predictors. Conversely, in a cohort of 111 patients, use of general anesthetics did not have any impact on mortality; here again the patients were evaluated only in ICU settings and interaction with SE refractoriness was not assessed [12]. Finally, a study by the same group recently showed that use of anesthetic agents is related to worse outcome; again, this analysis was limited to an ICU setting [13]. These divergent observations and the related methodological limitations (including a retrospective approach in most studies) prevent a conclusive judgment upon the impact of coma induction on SE outcome, independently from the underlying cause and the severity of the episode.

The objective of this study was to assess the specific impact of TC on prognosis of patients with SE, without restriction to ICU, after adjustment for the most important prognostic factors.

## **Material and Methods**

### *Cohort definition*

We included consecutive adult patients (older than 16 years old) with SE, admitted to our center between April 1, 2006 and July 30, 2013 (88 months), who were prospectively enrolled in our registry that received full approval from our Ethic commission. Cases with postanoxic etiologies were not enrolled in our registry. SE was defined as the occurrence of continuous seizures or repetitive seizures between which there is incomplete recovery of baseline clinical conditions for  $\geq 30$  min (until 2008) and for  $\geq 5$  min (since 2008). SE episodes were clinically diagnosed by neurology consultants and confirmed with electroencephalogram (EEG) studies, which was mandatory for non-convulsive forms. Further details on this registry have been published previously [6]. This study considered only incident cases of SE which lasted  $\geq 30$  min, in order to avoid over-representation of certain individuals and include only episodes with consistent prognostic implications.

### *Variables*

Age, gender, and history of previous seizures were prospectively recorded on admission. Etiology leading to death if not specifically treated was categorized as “potentially fatal” as previously detailed [15]. Level of consciousness before treatment was categorized as alert, confused or somnolent (arousable towards a clear clinical contact), stuporous (arousable, but without contact), and comatose; the latter two were classified as “severe impairment of consciousness”. Type of SE was defined by the worst clinical seizure in the given episode and classified, in increasing order of severity, as simple partial (focal without consciousness impairment), absence, myoclonic (related to genetic generalized epilepsy), complex partial (focal with consciousness impairment), generalized convulsive SE (GCSE), or non-convulsive SE in coma (NCSEC). GCSE episodes were further dichotomized into “proper” GCSE (those

which presented prolonged generalized convulsive seizures up to the SE diagnosis and treatment) and “GCSE then focal” (those with focal seizures without coma on diagnosis, but having presented an earlier generalized convulsion during the same episode), as we hypothesized that these two forms might have different prognostic implications. The SE severity score (STESS), a validated clinical scoring system considering age, worst seizures type, level of consciousness impairment, and history of previous seizures, was calculated for each patient on admission [16, 17].

We prospectively recorded use of therapeutic coma for SE treatment, specific anesthetic agents administered in each episode, and treatment latency (representing the best estimated time from SE onset to administration of the first medication and dichotomized at 1 hour following the beginning of the SE episode). Therapeutic coma was a clinically driven endpoint, monitored by EEG (with seizure suppression, or burst suppression, as target), and it was accomplished using anesthetic drugs as continuous intravenous drips. Our hospital is a third level center including a multidisciplinary ICU; patients with SE are mostly treated in the neurology ward (intermediate care unit) and admitted to the ICU if they need mechanical ventilation. The main clinical outcome, prospectively assessed at hospital discharge, was categorized into three groups: return to baseline, new disability (defined as new neurological impairment, as compared to the situation before the incident SE episode), or death.

By screening the computerized hospital database, medical comorbidities were retrospectively retrieved after discharge using the 17-items version of the Charlson Comorbidity Index (CCI), using International Statistical Classification of Disease and Related Health Problems, 10<sup>th</sup> Revision (ICD-10) coding algorithms [18, 19]; medical conditions considered as SE etiology for the specific episode were excluded from CCI, in order to avoid redundancy. Duration of acute hospital stay (defined as ICU and acute neurology ward stay) was also retrospectively retrieved in selected patients (see below), as was the occurrence of infectious complications requiring

antibiotics (classified into respiratory tract, urinary tract, bloodstream, or others) arising during SE treatment (infections occurring prior to SE or after SE treatment were not considered).

### *Statistical analysis*

The association between potential predictors and clinical outcome was analyzed using univariable multinomial logistic regressions. Multinomial (polytomous) logistic regression fits maximum likelihood models with discrete dependent variables, when the dependent variable takes on more than two outcomes and the outcomes have no natural ordering, as in the present study (**see suppl. material**). Outcome prognosticators with a  $p < 0.05$  were used in a backward procedure to fit a multivariable multinomial model. Results were described with relative risk ratios (RRR) and 95% confidence intervals (CI). We conducted analyses in the complete cohort, as well as in patients with GCSE “proper” or NCSEC vs. other SE forms.

Incidence of infectious complications was analyzed in a nested case-control assessment comparing all patients managed with TC and a control group of the same number of subjects treated without TC, matched for outcome, potentially fatal etiology, STESS, and CCI; results are given in odds ratio (OR) and 95% CI. The same approach was used to analyze the length of hospital stay using a Wilcoxon test; patients who died were excluded from this analysis, in order to avoid bias of shorter hospitalization. We chose to adjust for the aforementioned variables in order to specifically address the role of TC (exposure) on infections, respectively duration of in-hospital stay (outcomes), as clinical outcome may confound these relationships. The use of specific anesthetic drugs for coma induction was investigated with a Fisher’s exact test comparing the three outcome groups. Analysis was performed using the Stata software version 12 (College Station, TX); significance was considered at  $p < 0.05$ .



## Results

During the 88 months study period, we identified 467 incident episodes of adult SE lasting  $\geq 30$  min (representing 77.2% of 606 events in our registry; 52 episodes lasting  $< 30$  minutes and 86 recurrent episodes were excluded). Mean age was 60.3 years (SD  $\pm$  18.6) and 228 were women (48.8%). An overview of the clinical characteristics of patients according to functional outcome is presented in **Table 1**. At hospital discharge, half of patients returned to baseline conditions (51.0%), one-third had a new disability (34.7%), and mortality occurred in 14.3%. Fifty subjects (10.7%) were managed with therapeutic coma. Of the 67 patients who died, 23 died during SE and 7 had anesthetic treatments (4 propofol, 3 thiopental). A potentially fatal etiology was identified in 237 episodes; the most frequent occurrences were 50 (21.1%) primary brain tumors (mostly glioblastoma multiforme), 44 (18.6%) intracranial hemorrhages, 35 (14.8%) metastatic brain tumors, and 22 (9.3%) encephalitis or meningoencephalitis. On univariable analysis, worse outcome occurred more frequently in elderly subjects, as well as in patients having no history of previous seizures, a potentially fatal etiology, a severe impairment of consciousness, a higher STESS, a higher CCI, and TC for SE treatment.

The most common forms of SE encountered in our cohort were complex partial SE and “proper” GCSE (representing each about one third of the cohort); clinical characteristics of patients according to TC is shown in **Table 2**. Of note, there was no significant difference among the three outcome groups concerning the specific anesthetics agents used for coma induction (**Table 3**).

The multivariable model showed that the risk for new disability was independently higher in patients with increasing age, lack of previous seizures, a potentially fatal etiology, and TC. Furthermore, age, potentially fatal etiology, STESS, CCI, and TC were independently associated with mortality (**Table 4**). The relationship between these predictors and mortality was

also explored in the subgroups of patients with “proper” GCSE and NCSEC, versus other SE forms (**Figure 1**). After adjustment for the other predictors, TC for SE treatment was significantly related to outcome in both groups, but the effect magnitude tended to be higher among patients with complex partial SE forms at the time of treatment initiation.

Regarding the nested case-control assessment, among the 50 patients treated with TC the incidence of infectious complications was higher than in the 50 matched controls (31 vs. 15, OR=3.81, CI (95%): 1.66-8.75). Most (38; 64.4%) were lower respiratory tract infections, followed by urinary tract (11; 18.6%), and sepsis (10; 17%; some were combined in the same patient). Moreover, the median acute hospital stay was significantly longer in the 37 patients discharged alive and managed with this approach, than in the control group composed of 37 matched surviving subjects (16 days [range: 2-240] vs. 9 days [range: 1-57],  $p < 0.001$ , Wilcoxon).

## Discussion

The principal finding of this study is that TC administered for SE treatment is associated with a worse clinical outcome, including mortality, after taking into account the etiology and severity of the underlying condition; this relationship (Class III evidence) appears stronger in patients with forms of SE other than “proper” GCSE and NCSEC. In addition, subjects treated with this approach displayed higher infection rates, and longer acute hospital stay when discharged alive.

TC is advocated in current guidelines for management of SE, although its impact on functional outcome has not been clearly established, and somewhat surprisingly has received relatively little attention to date. This approach has been reported to be related to worse prognosis [10, 13], especially if lasting for many days [11], but not invariably [12] (although in this study interaction with SE refractoriness was not assessed). All these analyses had a retrospective

design and findings were not adjusted for all known outcome predictors, especially potentially fatal etiology; it is also at times unclear how recurrent cases were handled. Moreover, in three of those studies [11][12, 13], the analyzed cohort was exclusively composed of patients seen in ICUs, thus potentially limiting the generalizability; this is highlighted by the higher rate of administration of anesthetic agents (33%-87%) and prevalence of GCSE and NCSEC (46%-92%) as compared to the present cohort (11%, respectively 46%).

In the present study, the prognostic impact of TC in 467 consecutive adult patients with incident SE was investigated after adjustment for all major prognostic factors, such as etiology [15, 20, 21], STESS (including age, seizures type, consciousness impairment and history of previous seizures) [16, 17], and comorbid conditions assessed with the CCI [22, 23]; of note, apart from the CCI, the aforementioned variables were recorded prospectively. The combination of these variables has recently been shown to account for more than 90% of the mortality prediction [24]; their predictive robustness is consistently found across studies [25], and seems further confirmed by our findings. We also adjusted for age and lack of previous seizures. TC was significantly related to outcome in the whole cohort, and this relationship turned out to be even more important in the subgroup of patients with forms of SE others than “proper” GCSE or NCSEC: the vast majority of patients in this group were diagnosed with complex partial SE, an SE form felt to be less dangerous in terms of prognostic implication [26-28].

There is an ongoing lively debate among experts about the need to proceed quickly to coma induction in patients with “non-convulsive” SE (including complex partial) [29]; some recent guidelines indeed recommend intensive care treatment with TC for refractory SE, without specifying whether specific forms need an adapted treatment [5]. The present finding suggests in fact that this approach may prove especially harmful in such patients. To our knowledge, this is the first study investigating in detail the impact of TC on prognosis focusing on different forms

of SE classified by semiology. Particularly, we differentiated “GCSE then focal” (those with focal seizures without coma on diagnosis, but having presented previously a generalized convulsion during the same episode) from “proper” GCSE (those presenting with prolonged generalized convulsions up to the SE diagnosis and treatment), as we hypothesized that the former might represent a form of SE with prognostic implications similar to complex partial SE. Our results, added to the aforementioned studies [10, 13][11], seem thus to offer a rationale corroborating a relatively conservative therapeutic approach in patients without “proper” GCSE or NCSEC, in line with several expert opinions and recommendations suggesting to try additional non-sedating antiepileptic drugs before considering coma induction in these patients [4, 30-32].

A potential consequence of using TC relates to a higher risk of complications, such as infections, and longer hospitalizations. A recent study considering 160 subjects with SE in an ICU environment showed that infections were related to longer SE duration, longer ICU stay, higher risk of RSE, and higher mortality; the overall infection rate was 23% [33]. This was confirmed in the recent analysis by the same group[13]. Indeed we also observed a significant higher infection rate in patients treated with TC. Hospitalization length has been suggested to increase in SE patients needing airway intubation [34]. Moreover, among 54 patients with RSE, mean duration of coma was 11.0 days and mean hospital stay was 27.7 days [11]; and recently a longer hospitalization in patients treated with coma induction was showed [13], but without accounting for bias resulting from mortality. In our nested case-control study, acute hospitalization was significantly longer among surviving patients treated with TC as compared to matched controls. This finding implies potential major practical consequences, since prolonged hospitalization may expose patients to medical complications [33] and induce additional health care costs.

Our study has of course limitations. First, it is based on a single tertiary center cohort, and some data (such as CCI, acute hospital stay, and infection rates) were retrospectively retrieved.

However, we used a prospective registry for all other data (representing the most important prognostic variables), with homogeneous assessment criteria over the entire recruitment period, and the retrospectively added data were recorded by the same author (NAM), elements that in our view corroborate its internal validity. Moreover, to the best of our knowledge our study represents the largest cohort of SE adult patients, with the advantage of being representative of the SE population seen in a hospital, as it was not restricted to particular SE forms or an ICU environment: while of course patients with mechanical ventilation are found in the ICU, subjects with refractory SE managed outside the ICU were included in this study, as they represent a situation found in clinical practice (in fact, in our center patients not needing mechanical ventilation are mostly managed in intermediate care units). Second, as TC allocation was not randomized, we cannot formally exclude additional, not yet identified confounding factors. Particularly, we acknowledge that patients treated with TC were probably felt more ill, in some way that might not always have been accounted for by the analyses. However, multivariate analyses were used to adjust for the most important known outcome predictors (which together account for over 90% of SE prognosis [24]), reducing this risk. Third, we investigated the effect of TC on functional outcome at hospital discharge, but we cannot exclude that long term prognosis might have changed. Therefore, we also used mortality during the hospital stay, which represents a robust, non-debatable outcome. Additionally, our mortality rate of 14.3% corroborates the present findings, lying in the middle range as compared to several prospective, population-based studies [1, 2, 35]. Fourth, treatment latency represents an estimate, as SE onset is sometimes subtle or unclear (especially in patients with out-of-hospital SE onset); nonetheless, there was no significant difference among the outcome groups and it was not taken into account for the multinomial logistic regression (being nonsignificant in the univariable approach). Finally, we unfortunately do not have information regarding coma duration (but we retrieved hospitalization length in the nested case-control study), and specific EEG patterns,

and we did not adjust for treatment options before TC; however, medication appropriateness seems to play a negligible role in the prognosis of SE [24, 36].

## **Conclusion**

This study shows that TC is associated with mortality, poorer functional outcome, higher infection rates, and longer acute hospital stay after adjustment for the most important outcome predictors, and thus suggests caution in the straightforward use of this therapeutic approach, particularly in patients with complex partial SE at the moment of diagnosis. However, we acknowledge that factors like severe impairment of consciousness with loss of airways protection or durable generalized convulsive seizure leading to neuronal injury may direct the risk-benefit scale in favor of TC. Accordingly, the use of this approach for patients with GCSE or NCSEC appears fully justified. Multicenter, prospective studies are needed to better identify which further category of SE patients would take the best advantage from this approach, since the feasibility of a randomized trial in this setting unfortunately appears very unlikely [37].

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**Table 1** Demographics and clinical characteristics of 467 patients with incident status

epilepticus, according to clinical outcome at hospital discharge. Bold values are significant.

	Return to baseline (n = 238)	New disability (n = 162)	Death (n = 67)	New disability vs. Return to baseline RRR, CI (95%), P value	Death vs. Return to baseline RRR, CI (95%), P value
Age (years; mean, $\pm$ SD)	54.9 $\pm$ 18.9	65.3 $\pm$ 16.4	67.5 $\pm$ 17.1	<b>1.03, (1.02-1.05), P&lt;0.001</b>	<b>1.04, (1.02-1.06), P&lt;0.001</b>
Female gender (n = 228)	112 (47.1%)	84 (51.8%)	32 (47.8%)	0.83, (0.55-1.23), P=0.347	0.97, (0.56-1.67), P=0.919
Previous seizures (n = 199)	138 (58.0%)	42 (25.9%)	19 (28.4%)	<b>0.25, (0.16-0.39), P&lt;0.001</b>	<b>0.29, (0.16-0.52), P&lt;0.001</b>
Potentially fatal etiology (n = 237)	83 (34.9%)	100 (61.7%)	54 (80.6%)	<b>3.01, (1.99-4.56), P&lt;0.001</b>	<b>7.76, (4.00-15.03), P&lt;0.001</b>
Proper GCSE or NCSEC (n = 180)	92 (38.7%)	59 (36.4%)	29 (43.3%)	0.91, (0.60-1.37), P=0.651	1.21, (0.70-2.10), P=0.494
Severe impairment of consciousness (n = 257)	119 (50.0%)	89 (54.9%)	49 (73.1%)	1.22, (0.82-1.82), P=0.332	<b>2.72, (1.50-4.95), P=0.001</b>
STESS (median, [range])	2 [0;5]	3 [0;6]	3 [1;6]	<b>1.61, (1.38-1.89), P&lt;0.001</b>	<b>2.09, (1.66-2.62), P&lt;0.001</b>
Charlson Comorbidity Index (median, [range])	0.5 [0;10]	1 [0;9]	3 [0;8]	1.10, (1.01-1.21), P=0.028	<b>1.29, (1.16-1.44), P&lt;0.001</b>
Treatment latency > 1 hour (n = 312)	150 (63.0%)	113 (69.8%)	48 (71.6%)	1.35, (0.88-2.07), P=0.165	1.48, (0.82-2.68), P=0.193
Therapeutic coma (n = 50)	10 (4.2%)	27 (16.7%)	13 (19.4%)	<b>4.56, (2.14-9.71), P&lt;0.001</b>	<b>5.49, (2.29-13.18), P&lt;0.001</b>

CI = confidence interval; RRR = relative risk ratio; GCSE = generalized convulsive status epilepticus; NCSEC = nonconvulsive status epilepticus in coma; SE = status epilepticus; STESS = status epilepticus severity score

**Table 2** Demographics and clinical characteristic of patients with and without therapeutic coma.

	All patients (n = 467)	Patients without therapeutic coma (n = 417)	Patients with therapeutic coma (n = 50)
Age (years; mean, $\pm$ SD)	60.3 $\pm$ 18.6	60.7 $\pm$ 18.5	57.2 $\pm$ 19.2
Female gender	228 (48.2%)	204 (48.9%)	24 (48%)
Potentially fatal etiology	237 (50.7%)	210 (50.4%)	27 (54%)
STESS (median, range)	3 (0-6)	3 (0-6)	3 (1-6)
Type of SE			
- Simple partial	91 (19.5%)	91 (21.8%)	-
- Absence	7 (1.5%)	7 (1.7%)	-
- Myoclonic	1 (0.2%)	1 (0.2%)	-
- Complex partial	154 (33.0%)	144 (34.5%)	10 (20.0%)
- GCSE then partial	34 (7.3%)	30 (7.2%)	4 (8.0%)
- Proper GCSE	155 (33.2%)	130 (31.2%)	25 (50.0%)
- NCSEC	25 (5.4%)	14 (3.4%)	11 (22.0%)

SE = status epilepticus; GCSE = generalized convulsive status epilepticus; NCSEC = nonconvulsive status epilepticus in coma; STESS= status epilepticus severity score.

**Table 3** Clinical outcome in 50 patients categorized by the anesthetics used for therapeutic coma.

	Return to baseline (n = 10)	New disability (n = 27)	Death (n = 13)	P value (*)
Propofol	8 (80.0%)	26 (96.3%)	11 (84.6%)	0.186
Midazolam	2 (20.0%)	9 (33.3%)	4 (30.8)	0.844
Thiopental	1 (10.0%)	3 (11.1%)	3 (23.1%)	0.552
Ketamine	0 (0.0%)	2 (7.4%)	0 (0.0%)	0.713

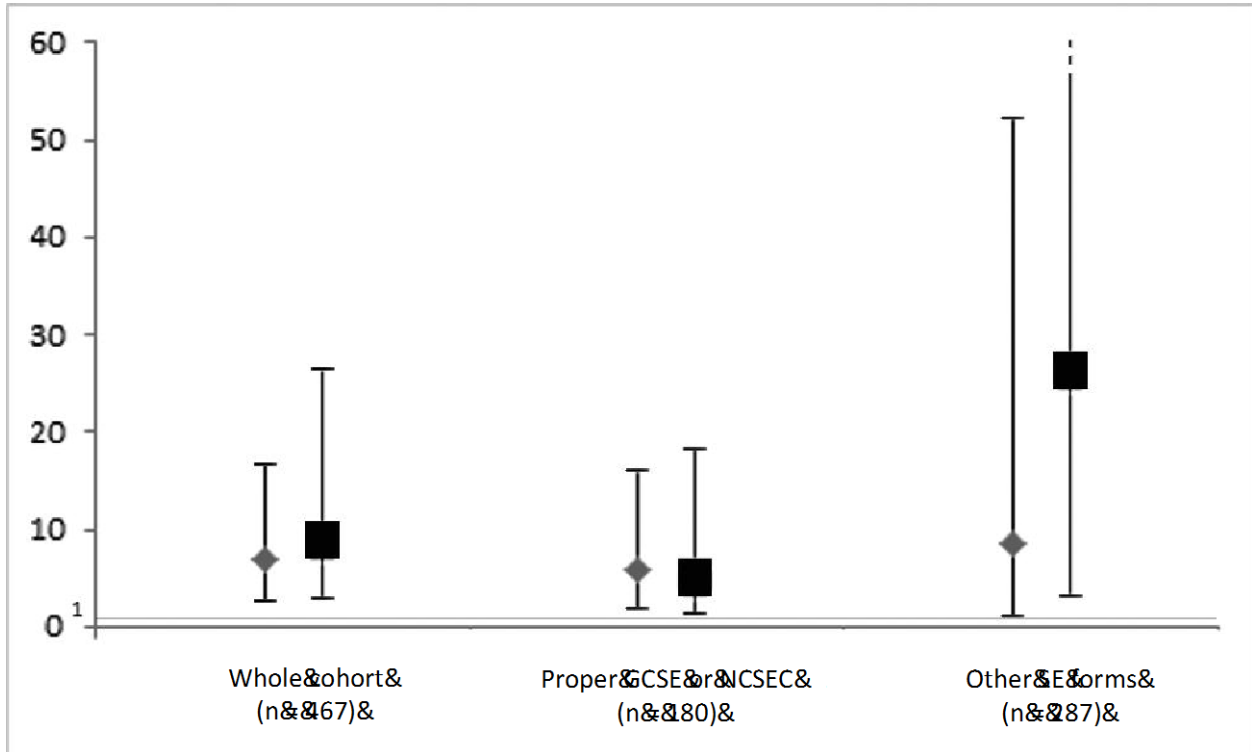
(\*) = Fisher's exact test

**Table 4** Identified variables associated with clinical outcome in 467 adults with incident SE from the fitted multivariable model. Results are given as relative risk ratio (RRR) and 95% confidence interval (CI), as compared to return to baseline clinical conditions. Variables with P<0.05 in the univariable analysis were retained for the multivariable assessment. Bold values are significant.

	New disability	Mortality
Age	<b>1.03 (1.01-1.05)</b>	<b>1.03 (1.01-1.05)</b>
Lack of previous seizures	<b>2.48 (1.49-4.15)</b>	1.35 (0.66-2.78)
Potentially fatal etiology	<b>2.72 (1.70-4.35)</b>	<b>7.2 (3.45-15.04)</b>
STESS	1.12 (0.92-1.38)	<b>1.56 (1.17-2.10)</b>
Charlson Comorbidity Index	1.02 (0.92-1.13)	<b>1.18 (1.05-1.33)</b>
Therapeutic coma	<b>6.86 (2.84-16.56)</b>	<b>9.10 (3.17-26.16)</b>

SE = status epilepticus; GCSE = generalized convulsive status epilepticus; NCSEC = nonconvulsive status epilepticus in coma; STESS = status epilepticus severity score

**Figure 1** Relative risk ratio of therapeutic coma for new disability and mortality, in the whole cohort, in patients with proper generalized convulsive or nonconvulsive SE in coma, and in patients with other SE forms.



SE = status epilepticus; GCSE = generalized convulsive status epilepticus; NCSEC = nonconvulsive status epilepticus in coma; grey diamonds = new disability; black squares = mortality.