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How to cite

MISIROCCHI, Francesco et al. Hypoalbuminemia in status epilepticus is a biomarker of short- and long-term mortality : A 9-year cohort study. In: European journal of neurology, 2025, vol. 32, n° 1, p. e16573. doi: 10.1111/ene.16573

This publication URL: https://archive-ouverte.unige.ch/unige:183295
Publication DOI: 10.1111/ene.16573

Received: 13 July 2024 | Accepted: 16 November 2024

DOI: 10.1111/ene.16573

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE

Hypoalbuminemia in status epilepticus is a biomarker of short- and long-term mortality: A 9-year cohort study

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Abstract

Background: Outcome prediction in Status epilepticus (SE) aids in clinical decision-making, yet existing scores have limitations due to SE heterogeneity. Serum albumin is emerging as a readily available prognostic biomarker in various clinical conditions. This study evaluates hypoalbuminemia in predicting short- and long-term mortality.

Methods: Observational cohort study including non-hypoxic SE adult patients admitted to the University Hospital of Geneva (Switzerland) between 2015 and 2023. Primary outcomes were in-hospital and 6-month mortality.

Results: Four hundred and ninety-six patients were included, 46 (9.3%) died in hospital; 6-month outcome was available for 364 patients, 86 (23.6%) were not alive at follow-up. Hypoalbuminemia was associated with older age and patients' comorbidities. Binomial regression showed an independent correlation between hypoalbuminemia and short- ($p=0.005$, OR = 3.35, 95% CI = 1.43–7.86) and long-term mortality ($p=0.001$, OR = 3.59,95% CI = 1.75–7.35).

The Status Epilepticus Severity Score (STESS) had an overall AUC of 0.754 (95% CI = 0.656–0.836) for predicting in-hospital mortality and of 0.684 (95% CI = 0.613–0.755) for 6-month mortality. Through an exploratory analysis, we replaced age with hypoalbuminemia in the STESS, creating the Albumin-STESS (A-STESS) score (0–6). The global A-STESS AUC significantly improved for both in-hospital (0.837, 95% CI = 0.760–0.916, $p=0.002$) and 6-month (0.739, 95% CI = 0.688–0.826; $p=0.033$) mortality prediction. A-STESS-3 cutoff demonstrated a strong sensitivity-specificity balance for both in-hospital (sensitivity = 0.88, specificity = 0.68, accuracy = 0.70) and 6-month (sensitivity = 0.67, specificity = 0.73, accuracy = 0.72) mortality.

Conclusions: Hypoalbuminemia is an easily measurable biomarker reflecting the overall patient's condition and is independently related to short- and long-term SE mortality. Integrating hypoalbuminemia into the STESS (A-STESS) significantly enhances mortality prediction. Future studies are needed to externally validate the A-STESS and evaluate the benefits of albumin supplementation in SE patient prognosis.

KEYWORDS
albumin, ICU, outcome, status epilepticus, STESS

INTRODUCTION

Status epilepticus (SE) is a neurological emergency with considerable heterogeneity in terms of etiology, semiology, and EEG findings, resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms that lead to abnormally prolonged seizures [1, 2]. SE outcome prediction provides pivotal prognostic information for clinicians and families, offering a practical way to stratify SE severity [3]. To date, several prognostic scores have been developed, mostly derived from patient's anamnestic data and SE features [4–7]. However, SE heterogeneity makes outcome prediction challenging, with the current available prognostic score without cutoff displaying a good sensitivity-specificity balance and/or relying on a variable not assessable at the early stages of SE [3, 8]. A new paradigm for SE prognostication should consider objective tools able to comprehensively assess patients at SE onset, and serum biomarkers are of particular interest.

Albumin is the most abundant serum protein, and its level is immediately available at low cost in almost all hospital-admitted patients, with hypoalbuminemia (HA) usually defined as a serum concentration < 35 g/L [9, 10]. Numerous studies across various clinical conditions, including cardiovascular, liver and renal diseases, cancer, and sepsis among others, have underscored the association between HA and poor outcomes [11–15]. HA predicts poor surgical outcomes [16, 17] and indicates reduced muscle mass and impaired immunity [15, 18]. Previous studies have established a general relationship between serum albumin level and SE outcome, albeit with a wide heterogeneity regarding selected cohorts, timing of serum measurements, definition of albumin levels as a continuous or binary variable, and adjustment for confounding factors [19–21]. Additionally, other reports have reported inconsistent findings [22, 23]. The aim of our study was to evaluate the relation between short- and long-term mortality and hypoalbuminemia at SE onset, assessing its utility in offering a comprehensive insight into patients' capabilities facing SE.

METHODS

Data collection and definitions

This is an observational single-center cohort study performed at the University Hospital of Geneva (HUG), a Swiss academic tertiary medical care center. The STROBE guidelines were followed to improve the quality of the study [24].

Data from all adult patients (aged ≥18 years) treated for SE at HUG between November 1st, 2015 and December 31st, 2023, were identified from an SE registry that was retrospectively collected until October 2021 and prospectively collected from November 2021.

Data were collected and managed with the password-encrypted online browser-based, metadata-driven database organizer REDCAP (Research Electronic Data Capture) [25]. SE Patients with SE following cardiorespiratory arrest were excluded, as this etiology is associated with a high mortality.

The following features were retrieved: age, sex, and main comorbidities (history of epilepsy, cerebrovascular disease, intracranial bleeding, brain injury, neurodegenerative disease, cardiopathy, pulmonary disease, peripheric vascular disease, liver disease, renal disease, diabetes, tumor). The following laboratory data were collected: Hematocrit, Leukocytes [10^9/L], Neutrophils [10^9/L], Thrombocytes [10^9/L], Albumin [g/L], Creatinine [umol/L], Bilirubin [umol/L], Urea [umol/L], C-reactive protein (CRP) [mg/L], pH, Sodium [mmol/L], Potassium [mmol/L].

SE etiology, semiology, and duration were also collected.

All laboratory data were assessed as close to SE onset as possible: for patients admitted for SE, the first laboratory tests were considered, for patients developing SE after hospital admission the laboratory test most closely related to SE begin were assessed. Following our hospital laboratory cutoffs, serum albumin level was defined as abnormal if <35 g/L, creatinine if >106umol/L, bilirubin if >25umol/L, and CRP if >10 mg/L. We considered only laboratory data retrieved within the first 24 h from SE onset.

SE types were defined as recommended by the current guidelines of the International League Against Epilepsy (ILAE) [1]. SE etiology was defined as acute symptomatic, remote symptomatic, progressive symptomatic, and unknown [1].

The Charlson Comorbidity Index (CCI, range 0–37), the Status Epilepticus Severity Score (STESS, range 0–6), and the Epidemiology-Based Mortality Score in Status Epilepticus (EMSE) were calculated to quantify comorbidity burden and illness severity, respectively [7, 26, 27]. CCI contains 19 issues (diabetes with diabetic complications, congestive heart failure, prior myocardial infarction, peripheral vascular disease, cerebrovascular disease, dementia, rheumatologic disease, chronic pulmonary disease, mild and severe liver disease, hemiplegia, renal disease, leukemia, lymphoma, cancer with and without metastases, peptic ulcer disease and acquired immunodeficiency syndrome), weighted according to their influence on 10-years mortality. STESS relies on age (65 years or older: 2 points), previous history of seizures (no previous seizures: 1 point), severity of seizure type (generalized convulsive: 1 point; non-convulsive SE in coma: 2 points), and level of consciousness (stuporous or comatose: 1 point) [7]. EMSE includes expected mortality rates for different ages, etiologies of SE, comorbidities, and EEG variables [5]. EEG data were not retrieved in our dataset; thus, we calculated a shorter EMSE version which considers only etiology, age, and level of consciousness (EMSE-EAC) [8].

SE duration was defined as the period between SE diagnosis and the clinical and/or EEG evidence of seizure termination, as previously

described [28, 29]. The time of SE onset was clinically defined for SE with prominent motor symptoms and electroencephalogram-defined (according to the Salzburg Criteria and the 2021 American Clinical Neurophysiology Society terminology) for patients with NCSE [30, 31]. Patients with SE were monitored with continuous EEGs or intermittent spot EEGs. Continuous EEGs were performed daily for at least 12 h per day and spot EEGs for at least 30 min every 12 h. Thereby, the calculated SE duration represents an approximation with a maximum inaccuracy of 12 h. For patients treated with anesthesia to achieve an EEG seizure-free pattern, the duration of SE was determined as the period from seizure onset until the establishment of an EEG seizure-free pattern, if the patient showed no relapse into SE after weaning from anesthetics [32]. Six-month mortality was assessed based on hospital and national death registries.

Outcomes

Primary outcomes were in-hospital and 6-month mortality.

Secondary outcomes were patients' features related to reduced serum albumin.

Statistics

Univariable comparisons were performed by the $\chi 2$ test for categorical variables. For continuous variables, the Shapiro–Wilk test was used to distinguish between normally and not normally distributed variables. Normally distributed variables were analyzed with the Student *t*-test, whereas variables violating the normal distribution were analyzed with the Mann–Whitney *U* test. For multiple comparisons, the level for significance was adjusted using the Bonferroni approach.

To assess independent association with primary outcomes, multivariable binomial regression models were computed to a stepwise selection approach considering all variables significantly related to outcomes at univariate analysis after Bonferroni correction together with EMSE-EAC and STESS features, assessing potential multicollinearity through Variance Inflation Factors (VIF) and defining collinearity a VIF value >4.

Receiver operating characteristic (ROC) curves were generated to determine EMSE-EAC and STESS capacity for in-hospital and 6-month mortality prediction. Sensitivity (SE), specificity (SP), positive and negative predictive values (PPV and NPV) and number of accurately classified patients (accuracy) for the two suggested STESS cutoff (STESS-3 and STESS-4) were calculated.

Through an exploratory analysis, we recalculated the STESS replacing age with serum albumin and attributing 2 points for HA (<35 g/L). The rationale behind this decision is twofold. Clinically, age is the only STESS variable that is neither directly (level of consciousness, type of seizure) nor indirectly (history of seizures) related to SE itself, but rather reflects the patient's overall condition, like serum albumin. Statistically, HA is the strongest variable associated with in-hospital and 6-month outcome, with age > 65 years strongly associated with HA in univariate analysis. Two points for HA, analogous to the 2 points given for age > 65 years in the original STESS, ensuring that the maximum scores of both systems remain comparable. This approach improves clinical practicality and facilitates a more straightforward comparison between the two scoring systems. The new STESS score, the Albumin-STESS (A-STESS) performances for in-hospital and 6-month mortality prediction were evaluated through ROC curve analysis, assessing the area under the curve (AUC), as well as SE, SP, PPV, NPV, and accuracy. A-STESS AUC of ROC curves for both in-hospital and 6-month mortality were compared to EMSE-EAC and STESS AUC of ROC curves using DeLong test. All analyses were performed utilizing the Jamovi software (Jamovi, 2022 version, Sydney, Australia).

RESULTS

In-hospital and 6-month mortality

Among 540 consecutively identified patients treated for SE during the study period, 44 patients with SE after cardiac arrest were excluded. Thus, 496 patients were included in the analysis, 46 (9.3%) died in hospital. Six-month outcome was available in 364 (73.4%) patients, 86 (23.6%) of them was not alive at the date of follow-up.

Main demographic, laboratory, and SE-related patients' features are presented in Table 1. After Bonferroni correction, cardiopathy ($p = 0.001$), CCI ($p < 0.001$), albumin level ($p < 0.001$), HA ($p < 0.001$), elevated CRP ($p < 0.001$), NCSE with coma ($p < 0.001$), SE duration ($p < 0.001$), non-remote etiology ($p < 0.001$) were all related to in-hospital mortality.

Considering SE prognostic scores, EMSE etiology ($p < 0.001$), overall EMSE-EAC ($p < 0.001$), STESS history of seizures ($p = 0.001$), STESS worst seizure type ($p < 0.001$), STESS degree of consciousness ($p < 0.001$) and overall STESS ($p < 0.001$) were related to in-hospital mortality after Bonferroni correction.

At 6-months, age ($p < 0.001$), cardiopathy ($p < 0.001$), CCI ($p < 0.001$), albumin level ($p < 0.001$), HA ($p < 0.001$), elevated CRP ($p = 0.001$), NCSE with coma ($p < 0.001$), SE duration ($p < 0.001$), non-remote etiology ($p < 0.001$) were still related to mortality after Bonferroni correction.

Considering SE prognostic scores, EMSE etiology ($p < 0.001$), EMSE age ($p < 0.001$), overall EMSE-EAC ($p < 0.001$), STESS age ($p < 0.001$), STESS worst seizure type ($p < 0.001$), and overall STESS ($p < 0.001$) were related to 6-month mortality after Bonferroni correction.

Multivariate binomial regression assessing significant univariate results and SE prognostic score features (excluding albumin level and age as continuous variables due to collinearity [VIF >4]) revealed that STESS history of seizures ($p = 0.020$, odds ratio [OR] = 0.319, 95% confidence interval [CI] = 0.122–0.836), NCSE with coma ($p = 0.016$, OR = 4.41, 95% CI = 1.31–14.9) and HA ($p = 0.005$, OR = 3.35, 95% CI = 1.43–7.86) were independently associated with in-hospital mortality. EMSE age ($p = 0.004$, OR = 1.45, 95% CI = 1.14–1.97),

TABLE 1 Univariate analysis assessing demographic, laboratory data, status epilepticus (SE) features, and prognostic scores variables according to in-hospital and 6-month mortality.

	In hospital: 496 patients			6-month: 364 patients		
	Survival (450)	Death (46)	*p*	Survival (278)	Death (86)	*p*
Patients features						
Male: Female ratio	253:197	25.21	0.511	165:113	47:39:00	0.44
Age (M, ±SD)	61.6 (19.2)	69.7 (16.2)	0.005	59.3 (19.2)	71.2 (14.7)	**<0.001**
Comorbid (non-mutually excluded)						
Cerebrovascular Disease	68	8	0.683	40	17	0.236
Past Intracranial Bleeding	67	13	0.019	49	20	0.244
Past Brain Injury	42	3	0.527	30	5	0.171
Neurodegenerative Disease	42	5	0.735	28	10	0.68
Cardiopathy	52	13	**0.001**	29	22	**<0.001**
Pulmonary disease	36	10	0.002	22	15	0.011
Peripheric Vascular Disease	49	4	0.646	33	8	0.51
Liver Disease	37	4	0.912	25	9	0.682
Renal Disease	50	7	0.406	32	11	0.748
Diabetes	78	6	0.78	55	10	0.106
Tumor	109	18	0.027	69	35	0.004
CCI (M, ±SD)	3.9 (2.8)	5.6 (3.2)	**<0.001**	3.7 (2.9)	5.5 (3.0)	**<0.001**
Laboratory data at SE onset[a]						
Hematology (M, ±SD)						
Hematocrit	0.40 (0.07)	0.36 (0.07)	0.003	0.4 (0.08)	0.37 (0.07)	0.003
Leukocytes (10^9/L)	10.5 (5.5)	11.5 (6.2)	0.328	10.3 (5.4)	10.5 (5.8)	0.872
Neutrophils (10^9/L)	10.3 (13.0)	10.8 (5.9)	0.331	10.7 (16.4)	10.4 (6.1)	0.509
Thrombocytes (10^9/L)	236 (87)	226 (99)	0.837	234 (86)	221 (92)	0.642
Blood chemistry[b]						
Albumin (g/L) (M, ±SD)	39.1 (6.4)	34.0 (5.6)	**<0.001**	39.8 (6.7)	34.9 (5.8)	**<0.001**
Hypoalbuminemia	83	27	**<0.001**	46	43	**<0.001**
Creatinine elevated	63	12	0.068	40	18	0.112
Bilirubin elevated	20	2	0.964	10	5	0.294
Urea elevated	63	13	0.013	38	21	0.008
C-reactive Protein (mg/L) (M, ±SD)	18.7 (57.8)	47.8 (74.7)	0.006	19.1 (65.8)	40.6 (69.8)	0.002
C-reactive Protein elevated	103	21	**<0.001**	73	34	**0.001**
Electrolytes (M, ±SD) (mmol/L):						
Sodium	138.7 (5.2)	140.1 (6.9)	0.152	138.6 (5.2)	140.1 (5.7)	0.135
Potassium	3.87 (0.6)	3.70 (0.6)	0.035	3.83 (0.5)	3.73 (0.5)	0.075
pH (M, ±SD)	7.34 (0.12)	7.36 (0.01)	0.625	7.35 (0.10)	7.36 (0.11)	0.126
SE features						
Focal NCSE without coma	139	13	0.713	84	31	0.309
With altered consciousness	111	10		64	24	
Without altered consciousness	28	3		20	7	
SE with prominent motor symptoms patients	288	19	0.003	183	36	**<0.001**
Convulsive	202	8		122	18	
Myoclonic	86	11		61	18	
NCSE with coma	23	14	**<0.001**	11	19	**<0.001**
Non-subtle	11	11		8	4	
Subtle	12	3		3	15	

TABLE 1 (Continued)

	In hospital: 496 patients			6-month: 364 patients		
	Survival (450)	Death (46)	*p*	Survival (278)	Death (86)	*p*
Days SE duration (M, ±SD)	1.6 (3.4)	3.6 (3.5)	**<0.001**	1.6 (3.4)	3.4 (1.8)	**<0.001**
SE etiology:						
Acute symptomatic	130	20	0.04	73	35	0.01
Remote symptomatic	190	7	**<0.001**	136	17	**<0.001**
Progressive symptomatic	74	13	0.045	46	25	0.01
Unknown	56	6	0.907	23	9	0.53
EMSE-EAC and STESS features						
EMSE etiology (M, ±SD)	12.1 (7.7)	18.1 (8.1)	**<0.001**	11.9 (7.6)	15.7 (8.3)	**<0.001**
EMSE age (M, ±SD)	6.0 (2.3)	7.3 (2.6)	0.005	5.6 (2.8)	7.4 (2.5)	**<0.001**
EMSE comorbidities (M, ±SD)	17.5 (20.4)	29.5 (26.2)	0.005	18.0 (20.5)	27.8 (25.2)	0.003
EMSE-EAC total (M, ±SD)	29.6 (22.3)	47.6 (25.3)	**<0.001**	29.9 (22.5)	43.5 (25.1)	**<0.001**
STESS History of seizures: yes	229	12	**0.001**	148	30	0.003
STESS Age > 65; yes	226	32	0.012	123	59	**<0.001**
STESS Worst seizure type						
Generalized convulsive	220	14	**<0.001**	132	26	**<0.001**
NCSE in coma	25	15		12	20	
STESS degree of consciousness: stuporous or comatose	215	34	**<0.001**	128	51	0.039
STESS total (M, ±SD)	2.5 (1.5)	3.8 (1.5)	**<0.001**	2.4 (1.5)	3.4 (1.6)	**<0.001**

Note: Level for significance was adjusted to <0.0018 after correction for multiple comparisons (Bonferroni). Significan values after correction are highlighted in bold.

Abbreviations: CCI, Charlson comorbidity index; EMSE, Epidemiology-Based Mortality Score in Status Epilepticus; EMSE-EAC, EMSE etiology age and comorbidity; M, mean; NCSE, non-convulsive SE; SD, standard deviation; SE, status epilepticus; STESS, status epilepticus severity score.

[a]Hematocrit assessed in 450 patients (pts) and 329pts, Leukocytes in 480pts and 354pts, Neutrophils in 181pts and 124pts, Thrombocytes in 462pts and 338pts, C-reactive protein in 422pts and 311pts, Albumin in 428pts and 324pts, Creatinine in 466pts and 341pts, Bilirubin in 402pts and 291pts, Urea in 442pts and 323pts, Sodium 397pts in 278pts, Potassium in397pts and 278pts, pH in 372pts and 261pts.

[b]Albumin <35 g/L, Creatinine >106umol/L, Bilirubin >25umol/L, Urea >7.5uml/L, C-reactive protein >10 mg/L.

non-remote symptomatic SE etiology ($p = 0.008$, OR = 2.89, 95% CI = 1.32–6.36), NCSE with coma ($p = 0.005$, OR = 5.60, 95% CI = 1.68–18.6) and HA ($p.001$, OR = 3.59, 95% CI = 1.75–7.35) were associated with 6-month mortality. Results are displayed in Table 2.

HA was associated with age ($p < 0.001$) and age > 65 years old ($p < 0.001$), cardiopathy ($p < 0.001$), pulmonary disease ($p < 0.001$), liver disease ($p < 0.001$), low hematocrit ($p < 0.001$), elevated bilirubin ($p = 0.005$) urea ($p < 0.001$) and CRP ($p < 0.001$), higher CCI ($p < 0.001$), higher EMSE comorbidity burden ($p < 0.001$), and both in-hospital and 6-month mortality (both $p < 0.001$) (Table 3).

EMSE-EAC, STESS, and Albumin-STESS (A-STESS)

Considering only patients with available serum albumin level, in-hospital outcome and 6-month outcome were retrievable in 428 and 324 patients, respectively. For predicting in-hospital mortality, EMSE-EAC AUC was 0.713 (95% CI: 0.631–0.795), and STESS AUC was 0.754 (95% CI: 0.656–0.836). The cutoff of 3 (STESS≥3) (Youden's Index [YI] = 0.401) showed a sensitivity of 0.875 and a specificity of 0.526; the cutoff of 4 (STESS≥4) (YI = 0.350) a sensitivity of 0.600 and a specificity of 0.750. For predicting 6-month mortality, EMSE-EAC AUC was 0.664 (95% CI: 0.578–0.750), STESS AUC was 0.684 (95% CI: 0.613–0.755). The cutoff of 3 (STESS≥3) (YI = 0.225) showed a sensitivity of 0.699 and a specificity of 0.582; the cutoff of 4 (STESS≥4) (YI = 0.225) a sensitivity of 0.45, and a specificity of 0.773.

Through a hypothesis-generating approach we replace age to albumin level in the STESS, creating the Albumin-STESS, A-STESS (range 0–6) and attributing 2 points for HA.

Global A-STESS AUC significantly improved for both in-hospital (0.837, 95% CI: 0.760–0.916; $p = 0.002$) and 6-month (0.739, 95% CI: 0.688–0.826; $p = 0.033$) mortality prediction. Moreover, the

TABLE 2 Stepwise binomial logistic regression analysis result assessing variables significant at univariate analysis (after Bonferroni correction), Status Epilepticus Severity Score (STESS), and Epidemiology-Based Mortality Score in Status Epilepticus (EMSE-EAC) features according to in-hospital and 6-month mortality.

	In hospital mortality				6-month mortality			
			95% CI				95% CI	
	p	OR	Lower	Higher	*p*	OR	Lower	Higher
STESS Age > 65	0.356	0.621	0.226	1.71	0.520	1.29	0.592	2.82
STESS History of seizures	**0.020**	**0.319**	**0.122**	**0.836**	0.503	0.783	0.383	1.60
STESS Worst seizure type	0.248	0.578	0.229	1.47	0.624	1.15	0.657	2.02
STESS Degree of consciousness: stuporous or comatose	0.113	2.34	0.817	6.70	0.111	1.88	0.866	4.09
EMSE age	0.840	1.03	0.777	1.36	**0.004**	**1.45**	**1.14**	**1.97**
EMSE etiology	0.085	1.05	0.994	1.102	0.762	1.01	0.962	1.05
EMSE comorbidity	0.544	1.01	0.973	1.05	0.182	0.976	0.904	1.01
Comorbidity: Cardiopathy	0.165	2.50	0.716	7.01	0.101	2.16	0.844	5.52
SE duration	0.488	0.989	0.963	1.02	0.944	1.01	0.967	1.04
Etiology: Non-Remote symptomatic	0.342	0.601	0.211	1.71	**0.008**	**2.89**	**1.32**	**6.36**
NCSE with coma	**0.016**	**4.41**	**1.31**	**14.9**	**0.005**	**5.60**	**1.68**	**18.60**
Hypoalbuminemia[a]	**0.005**	**3.35**	**1.43**	**7.86**	**0.001**	**3.59**	**1.75**	**7.35**
C-reactive Protein elevated[a]	0.748	1.66	0.456	2.96	0.715	1.14	0.557	2.35

Note: Signifcant variables are highlighted in bold.

Abbreviations: 95% CI, 95% confidence interval; CCI, Charlson comorbidity index; EMSE, Epidemiology-Based Mortality Score in Status Epilepticus; OR, odds ratio; SE, status epilepticus; STESS, status epilepticus severity score.

[a]Albumin <35 g/L, C-reactive protein >10 mg/L.

A-STESS 3 cutoff (A-STESS≥3) demonstrated a better balance of sensitivity and specificity for predicting both in-hospital (YI = 0.590, sensitivity = 0.88, specificity = 0.68) and 6-month (YI = 0.404, sensitivity = 0.67, specificity = 0.73) mortality, while preserving good accuracy (0.70 and 0.72, respectively).

Figure 1 displays global AUC curves for EMSE-EAC, STESS, and A-STESS for in-hospital and 6-month mortality. Table 4 and Figure 2 show STESS-3, STESS-4 and A-STESS-3 cutoffs performances.

Comparison of STESS-3, STESS-4, and A-STESS-3

STESS-3 versus A-STESS-3

Fourteen patients transitioned from being classified as low risk (STESS <3) to high risk (A-STESS ≥3). Among these, 2 out of 14 (14%) died in the hospital, and 4 out of 14 (29%) did not survive the 6-month follow-up. Conversely, 73 patients moved from being considered high risk (STESS ≥3) to low risk (A-STESS <3). Among them, only 2 out of 74 (3%) had an adverse outcome in the hospital, and 6 out of 54 (11%) had an unfavorable outcome at 6 months.

STESS-4 versus A-STESS-3

Sixty-five patients transitioned from being classified as low risk (STESS <4) to high risk (A-STESS ≥3). Among these, 11 out of 65 (17%) died in the hospital, and 16 out of 46 (35%) did not survive the 6-month follow-up. Finally, 37 patients moved from high risk (STESS ≥4) to low risk (A-STESS <3). Among them, only 2 out of 37 (5%) had an adverse outcome in the hospital, and 2 out of 27 (7%) had an unfavorable outcome at 6 months.

DISCUSSION

This study evaluated serum albumin level in predicting SE patient's outcome, revealing an independent association between HA at SE onset and short and long-term mortality. HA was associated with older age and a higher burden of comorbidities, as also reflected by CCI and EMSE comorbidity feature. By replacing age with HA into STESS (due to significant association between the two variables and their capacity of reflecting overall patients' status), we developed the A-STESS score, significantly improving the overall AUC for both short- and long-term mortality prediction, with the optimal cutoff was set at 3 (A-STESS≥3: mortality).

Currently, various prognostic scores exist to predict SE outcome; however, their practical benefit is limited, due to only acceptable predictive power, lack of generalizability, and signs of poor calibration [8]. Notably, the STESS, the most widely used prognostic score, lacks a single cutoff value that balances specificity and sensitivity. Specifically, STESS-3 has low specificity, while STESS-4 has low sensitivity in predicting poor outcome [8]. Additionally, current available SE prognostic scores rely on variables often not

TABLE 3 Univariate analysis of demographic features, laboratory data, and outcome of patients with normal (>35 g/L) and low (<35 g/L) albumin at Status Epilepticus (SE) onset.

	Normal albumin (318)	Low albumin (110)	*p*
Patients features			
Male: Female ratio	178:140	64:46:00	0.687
Age (M, ±SD)	59.4 (19.1)	70.7 (15.2)	**<0.001**
Age > 65 yrs	145	75	**<0.001**
Comorbid (non-mutually excluded):			
Cerebrovascular Disease	40	23	0.034
Intracranial Bleeding	47	22	0.199
Brain Injury	28	11	0.707
Neurodegenerative	25	15	0.073
Cardiopathy	32	24	**<0.001**
Pulmonary disease	17	22	**<0.001**
Peripheric Vascular Disease	32	15	0.301
Liver Disease	18	19	**<0.001**
Renal Disease	34	15	0.403
Diabetes	51	28	0.043
Tumor	74	31	0.302
CCI (M, ±SD)	3.5 (2.8)	5.2 (2.9)	**<0.001**
EMSE comorbidity (M, ±SD)	16.4 (19.8)	25.3 (24.0)	**<0.001**
Laboratory data at SE onset[a]			
Hematology (M, ±SD):			
Hematocrit	0.41 (0.07)	0.36 (0.07)	**<0.001**
Leukocytes (10^9/L)	10.7 (5.8)	10.4 (5.0)	0.599
Neutrophils (10^9/L)	10.8 (15.4)	9.4 (5.1)	0.89
Thrombocytes (10^9/L)	240 (85)	221 (104)	0.075
Blood chemistry[b]:			
Creatinine elevated	50	20	0.112
Bilirubin elevated	11	11	**0.005**
Urea elevated	44	32	**<0.001**
C-reactive Protein elevated	66	58	**<0.001**
Electrolytes (M, ±SD) (mmol/L):			
Sodium	138.9 (4.9)	138.4 (6.7)	0.501
Potassium	3.9 (0.6)	3.7 (0.6)	0.031
pH (M, ±SD)	7.33 (0.12)	7.37 (0.11)	0.02
Outcome			
In-hospital mortality	13	27	**<0.001**
6-month mortality[c]	30	43	**<0.001**

Note: Level for significance was adjusted to <0.006 after correction for multiple comparisons (Bonferroni). Significant values after correction are highlighted in bold.

Abbreviations: CCI, Charlson comorbidity index; M, mean, SD, standard deviation; SE, status epilepticus.

[a]Hematocrit assessed in 398pts, Leukocytes in 424pts, Neutrophils in 161pts, Thrombocytes in 408pts, C-reactive protein in 422pts and 311pts, Albumin in 428pts and 324pts, Creatinine in 466pts and 341pts, Bilirubin in 402pts and 291pts, Urea in 442pts and 323pts, pH in 372pts and 261pts, Sodium 397pts in 278pts, Potassium in397pts and 278pts.

[b]Creatinine >106umol/L, Bilirubin >25umol/L, Urea >7.5uml/L, C-reactive protein >10 mg/L.

[c]6-month mortality assessed in 324pts.

assessable at early SE stages, such as EMSE, and do not consider organ dysfunction and physiological reserve beyond the brain [3, 23]. Complex illness severity scores such as the Simplified Acute Physiology Score II (SAPS II) and the Acute Physiology and Chronic Health Evaluation II (APACHE II) are also available, but their performance is overall not superior to SE-specific tools, and they are

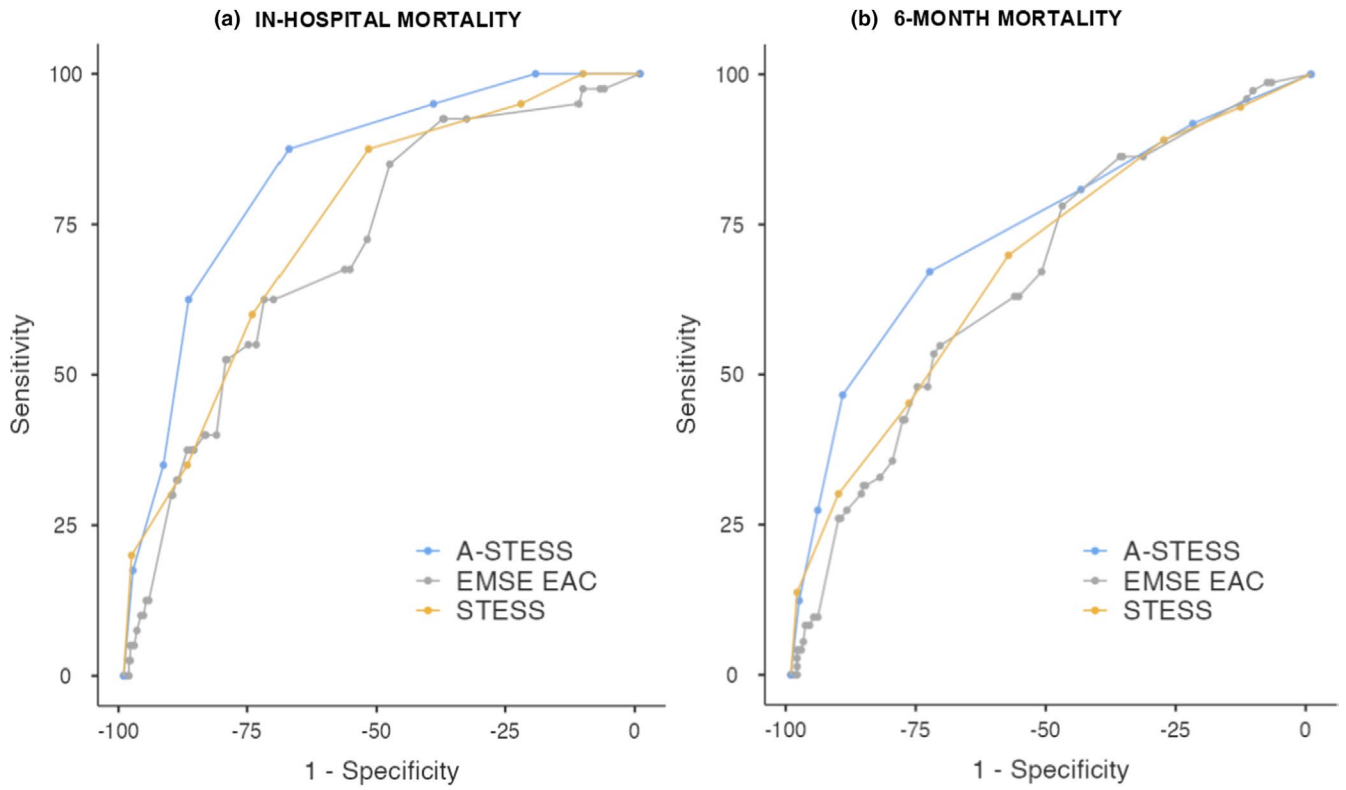

FIGURE 1 Combined receiver operating characteristic curves for both in-hospital (a) and 6-month (b) mortality of Status Epilepticus Severity Score (STESS), Epidemiology-Based Mortality Score in Status Epilepticus (EMSE-EAC) and Albumin-STESS (A-STESS).

	Sensitivity	Specificity	PPV	NPV	Accuracy
In-hospital mortality					
STESS-3	88%	52%	16%	97%	55%
STESS-4	60%	75%	19%	95%	72%
A-STESS-3	88%	68%	22%	98%	70%
6-month mortality					
STESS-3	69%	58%	32%	87%	60%
STESS-4	45%	77%	36%	83%	77%
A-STESS-3	67%	73%	42%	88%	72%

TABLE 4 Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy for both in-hospital and 6-month mortality of Status Epilepticus Severity Score (STESS) 3 and 4 cutoffs and albumin-STESS (A-STESS) 3 cutoff.

predominantly adopted in ICU setting, due to extensive data requirements and historical habits [33–35]. Blood and cerebrospinal fluid SE biomarkers, such as neuron-specific enolase, neurofilaments, glial fibrillary acid protein, and several others, have been increasingly investigated [36, 37]. However, these reflect neuronal and glial SE-induced injury and are independent of patient features. They are useful for grading SE severity, but their levels are highly dependent on sampling time, with current literature primarily based on case reports or small case series [36].

Our objective was to shift SE prediction paradigm assessing objective and easily measurable tools capable of providing a comprehensive understanding of the patient's resources in facing SE. Albumin plays a crucial role in numerous physiological functions, yet several pathological conditions can lead to low albumin levels, including nutritional deficiency, increased loss, impaired hepatic synthesis, and reduced production due to chronic inflammatory state [15, 18]. Therefore, albumin level at SE onset might represent a good indicator of the overall patient's resources, with HA as a marker of low physiological reserves. We found that HA correlated significantly with the presence of respiratory, liver, and heart diseases, as well as low hematocrit and elevated urea and CRP levels. Additionally, HA was associated with older age and a greater overall comorbidity burden, as represented by the CCI score and the EMSE comorbidity feature.

Some reports have addressed the relationship between serum albumin and SE outcome [19–23]. In a retrospective cohort study on 135 patients, albumin level both at hospital admission and SE onset was significantly associated with death in multivariate analysis,

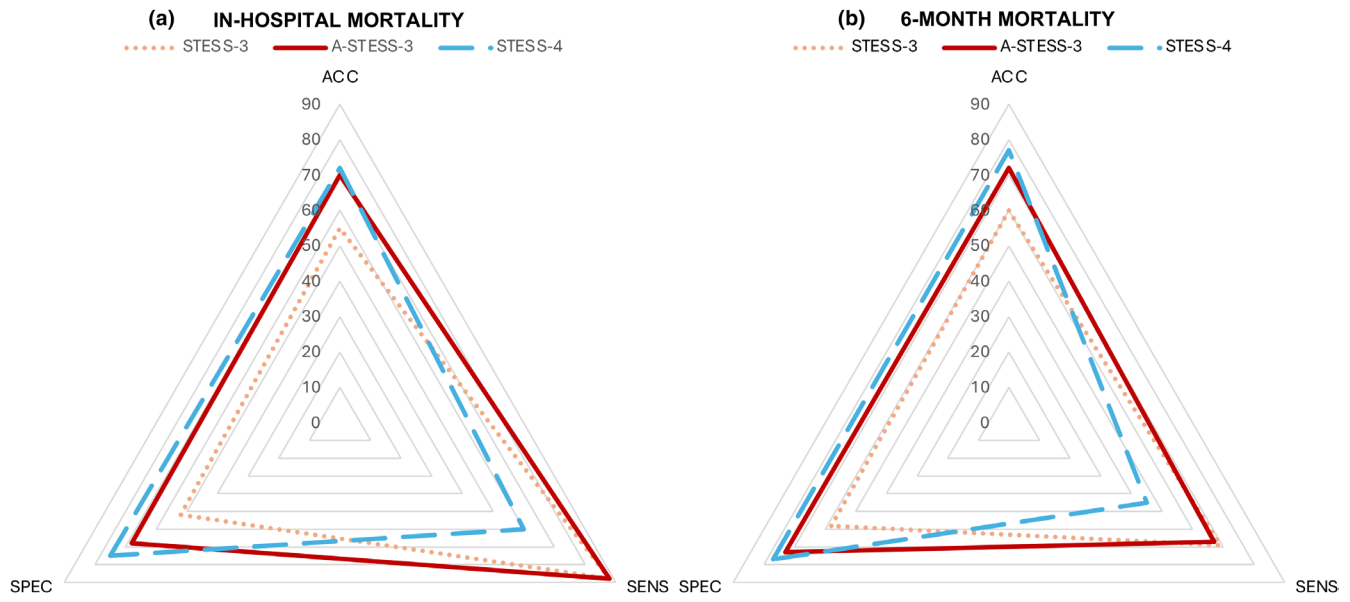

FIGURE 2 Predictive performances for in-hospital (a) and 6-month (b) mortality of STESS-3, STESS-4, and A-STESS-3. SENS: Sensitivity. SPEC: Specificity. PPV: Positive predictive value. NPV negative predictive value. ACC: Accuracy. STESS: Status epilepticus severity score. A-STESS: Albumin-STESS.

supporting our results [19]. In another study, low albumin within the first 24 hours of SE was related to in-hospital death at univariate analysis, but not after adjusting for levels of procalcitonin [22]. In two analyses considering only patients with convulsive SE (CSE), HA (assessed at admission in one study and at SE onset in the other) was an independent predictive factor for short-term mortality [20, 21]. Interestingly, HA was combined in a nomogram with other outcome-related variables to build a score for CSE functional outcome prediction at 3 months (global AUC 0.806 [95% CI: 0.683–0.923]) [21]. In contrast, a prospective study addressing a small cohort of 30 ICU-admitted patients with convulsive SE only did not find any relationship among serum albumin concentration at admission and SE outcome [23]. Up to now, the present study is to our knowledge the largest on HA and SE outcome, and underscores that HA is a relevant predictive parameter.

Differently from other studies, our results rely on a large and heterogeneous cohort of patients, evaluating both short- and long-term mortality. The assessment of albumin as a binary variable facilitated results interpretation, and we integrated HA into STESS, the most widely used and validated SE prognostic score, preserving its simplicity and ability of early stratification, differently from EMSE [7]. We replaced age with HA, given HA's significant correlation with older age and the fact that age was the only STESS variable reflecting overall patient status prior to SE. The A-STESS score significantly outperformed EMSE-EAC and the original STESS in predicting both in-hospital and 6-month mortality, with an A-STESS score of 3 achieving an excellent balance between sensitivity and specificity.

Albumin is a negative acute phase reactant, and HA was considered in previous SE studies as a direct measure of the SE-induced inflammation process [19–21, 23]. However, serum albumin assessment typically occurrs at SE onset or even at hospital admission [19–21, 23], while significant reduction requires time, primarily involving lowered albumin-RNA transcription in liver cells [38, 39]. Indeed, albumin concentration decreases during acute inflammation reaching its nadir approximately >120 h after the exposure to the inflammatory trigger, with no significant reduction in the first hours [38–40].

Albumin level at SE onset should, therefore, not be considered as merely reflecting the acute inflammatory syndrome induced by SE, but a good indicator of the overall patient's patho-physiological context and biological resources when facing SE. Notably, while both elevated CRP and low serum albumin level were related to mortality at univariate analysis, only HA was significantly associated with death after multivariate regression, both at hospital discharge and at 6-month follow-up.

The superior predictive capacity of the A-STESS score compared to the original STESS probably lies in its ability to better classify two distinct patient groups. On the one hand, it identifies older patients who are overall fit (i.e., healthy and without severe comorbidities) as being at low risk. On the other hand, it considers relatively younger patients as high risk if they have significant comorbidities and reduced physiological reserves to face SE.

Finally, we found an association between albumin levels and mortality but did not assess whether albumin supplementation could improve prognosis, as seen in other patient categories [41, 42], although sometimes with inconsistent results [43]. To date, the use of human albumin, due to its high cost, should be reserved for contexts where its effectiveness is well-established. Regarding SE specifically, it is likely that treatment would yield better results in patients with severe HA compared to those with levels just below the normal threshold. However, without prospective, ideally randomized, interventional trials, we cannot make any recommendations on this topic.

Our study has several limitations. First, it relies on an ambispective observational design with data derived from a single tertiary care center. Based on our findings, we considered HA as a biomarker of frailty, but we did not specifically evaluate any true measure of fragility, such as the fragility index [44]. There were gaps in data availability for albumin level and long-term outcome, potentially introducing a selection bias. Furthermore, we were unable to assess the correlation between serum albumin and functional outcome, as we only had information regarding long-term mortality.

Patients with acute infections at SE onset were not excluded, due to the limited number of patients (5% of the total cohort) and because our research question was the association between HA at SE onset and mortality, regardless of the presence of SE-related infection. However, this aspect possibly confounds the relationship between HA and baseline patient conditions. We did not conduct any longitudinal concentration assessments, preventing us from exploring the relationship between longitudinal albumin decrease and SE outcome.

Due to the lack of data, we did not compare A-STESS with the complete version of EMSE (requiring EEG features) and with modified STESS (mSTESS), incorporating baseline modified Rankin Scale (mRS) and raising the threshold age at 70 years [45]. However, the version of EMSE we used (EMSE-EAC) already includes the comorbidity variable along with a stratified representation of age. Despite this, A-STESS outperforms EMSE-EAC in predicting both in-hospital and 6-month mortality.

CONCLUSION

Hypoalbuminemia at SE onset is an easily measurable tool independently related to short- and long-term mortality in SE patients, and it might represent a good biomarker of overall patient's resources to survive SE. By integrating HA into STESS, we developed the A-STESS score, significantly enhancing its predictive capacity. Future prospective studies are mandatory to validate the promising predictive value of A-STESS, extend our findings to the functional outcomes of survivors, and explore the potential benefits of albumin supplementation in patients with severe HA.

AUTHOR CONTRIBUTIONS

Francesco Misirocchi: Conceptualization; investigation; writing – original draft; methodology; writing – review and editing; formal analysis. **Hervé Quintard:** Supervision; writing – review and editing; conceptualization. **Andrea O. Rossetti:** Conceptualization; writing – review and editing; supervision. **Irene Florindo:** Supervision; writing – review and editing. **Oana E. Sarbu:** Writing – review and editing; data curation. **Andreas Kleinschmidt:** Writing – review and editing; supervision. **Karl Schaller:** Supervision; writing – review and editing. **Margitta Seeck:** Supervision; writing – review and editing; conceptualization. **Pia De Stefano:** Conceptualization; investigation; methodology; writing – review and editing; writing – original draft; supervision; project administration; data curation.

ACKNOWLEDGEMENTS

FM is supported by the 2023 International Federation of Clinical Neurophysiology (IFCN) Research Fellowship Grant. PDS is supported by the 2022 Swiss League Against Epilepsy Research Support Prize.

FUNDING INFORMATION

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST STATEMENT

FM is supported by the 2023 International Federation of Clinical Neurophysiology (IFCN) Research Fellowship Grant. HQ declares no competing interests. AOR declares no competing interests. IF declares no competing interests. OES declares no competing interests. AK has received honoraria for consulting from Abbvie, EliLilly, Lundbeck, Mitsubishi Tanabe, Novartis, and TEVA that were paid to a teaching and research fund at the University Hospital Geneva. KS declares no competing interests. MS is a shareholder of Epilog NV (Ghent, Belgium). She received grants from the Swiss National Science Foundation (163,398, CRS115–180365). PDS was supported by the Swiss National Science Foundation (163,398, CRS115-180365) and is supported by the 2022 Swiss League Against Epilepsy Research Support Prize.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study protocol was reviewed and approved by the local ethic committee (CCER 2019-00836), and patient's consent was waived in compliance with the Declaration of Helsinki first published in 1964 and its following amendments.

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How to cite this article: Misirocchi F, Quintard H, Rossetti AO, et al. Hypoalbuminemia in status epilepticus is a biomarker of short- and long-term mortality: A 9-year cohort study. *Eur J Neurol*. 2025;32:e16573. doi:10.1111/ene.16573