



The Prevalence and Prognostic Value of Neuroimaging Abnormalities in the Acute Phase of Sepsis-Associated Encephalopathy



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Abstract

Objectives: Sepsis-associated encephalopathy (SAE) is the most common form of encephalopathy in the intensive care unit (ICU) today. However, little is known about the underlying pathogenesis and clinical significance of the brain changes associated with SAE. Using magnetic resonance imaging (MRI) and computed tomography (CT), the present study evaluated the spectrum of brain abnormalities in patients with SAE and examined whether these abnormalities predicted clinical features of SAE, ICU mortality, one-year mortality, and disability.

Methods: We examined clinical and radiological data from 60 consecutive adults admitted to the medical ICU without preexisting neurological conditions, who met criteria severe sepsis or septic shock and subsequently developed SAE. Neuroimaging attributes were rated by two radiologists using a standardized protocol.

Results: Common neuroimaging findings included periventricular and subcortical white matter lesions, cerebrovascular calcification, and lacunar infarction. By comparison, acute infarction, acute hemorrhage, cytotoxic edema, and vasogenic edema were less prevalent. Acutely altered mental status (e.g., delirium) was the most common form of SAE and was associated with greater cerebral atrophy ($p=.029$) and subcortical white matter lesion burden ($p=.010$) relative to patients presenting with new-onset of focal neurologic signs or new-onset seizure. Acute, but not chronic, neuroimaging findings were associated with risk for ICU mortality ($p=.026$), one-year mortality ($p=.016$), and disability ($p=.032$) after adjusting for potentially confounding variables.

Discussion: Though less common than chronic neuroimaging findings, acute neuroimaging abnormalities have prognostic significance as predictors of disability and survival in the first year following the development of SAE.

Keywords: Brain Disease; Brain Injuries, Acute; Neuroimaging; Critical Care; Sepsis; Shock, Septic

Introduction

Severe sepsis is a common form of critical illness that affects approximately 750,000 people in the USA annually [1]. Morbidity and mortality, especially within the first year after severe sepsis are exceedingly high, making sepsis the 10th leading cause of death in the USA [1,2]. Acute cognitive or neurologic dysfunction during sepsis, known collectively as sepsis-associated encephalopathy (SAE), is the most common form of encephalopathy in the intensive care unit (ICU) [3-5]. Although it remains unclear whether the pathological processes associated with neurologic and cognitive dysfunction during sepsis are fully reversible, SAE has been linked to a two-fold increase in mortality and elevated risk for long-term cognitive deficits [4,6,7]. Currently, the ability to successfully

treat and identify patients most vulnerable to SAE is limited by an incomplete knowledge of the underlying pathogenesis and neurobiology of this syndrome.

The current understanding of SAE is based largely on animal models and a set of descriptive case series [8-14]. To date, human studies of SAE have been limited by small sample size and the inclusion of heterogeneous patient groups with a range of medical and neurologic comorbidity. The only large neuroimaging study to examine brain changes in SAE found either leukoencephalopathy or ischemic stroke in approximately half of patients [5]. However, because this study did not make the distinction between acute and chronic neuroimaging abnormalities, the significance of

these findings remains unclear. To date, the prevalence of other clinically relevant neuroimaging abnormalities, such as cytotoxic and vasogenic edema, has not been examined in a large series of patients with SAE, significantly limiting the understanding of SAE pathogenesis. The link between SAE and mortality among septic patients also remains poorly understood. Although ischemic stroke has been associated with increased ICU mortality [5], it is currently unknown whether specific neuroimaging abnormalities observed during the acute phase of SAE are predictive of survival within the first year following ICU discharge, a period when mortality is as high as 50% for individuals who survive sepsis [2].

The goals of the current study were to extend the understanding of SAE by using MRI and CT to evaluate the prevalence and clinical significance of acute and chronic brain abnormalities in patients who developed cognitive or neurological dysfunction (i.e., altered mental status, focal neurologic sign, or seizure) during the acute phase of severe sepsis or septic shock. To this end, we first examined the prevalence of vasogenic and cytotoxic edema, hemorrhage, infarction, atrophy, arterial and venous calcification, and white matter lesions. Based on previous findings [15-17], white matter lesions, acute infarctions, and cerebral edema were expected to be most common. The second goal of this study was to examine the association between clinical features of SAE and neuroimaging attributes with the expectation that focal neurologic findings and *acutely altered mental status* would be associated with acute neuroimaging findings and elevated white matter lesion burden, respectively. Lastly, we tested the hypothesis that acute neuroimaging findings and elevated white matter lesion burden would be associated with greater risk of ICU mortality, one-year mortality, and disability.

Materials and Methods

Study Design and Population

This was a retrospective analysis of data collected from consecutive patients admitted to a 17-bed ICU at an academic medical institution in the greater New York metropolitan area between January 2012 and June 2015. The study protocol was reviewed and approved by the hospital's institutional review board; HIPAA compliance was maintained. Relevant medical, demographic, and treatment-related data were extracted from electronic medical records. Mortality data were obtained from health system records and the Social Security Death Index.

Eligible patients met the following criteria:

- a) Diagnosis of severe sepsis or septic shock according to International Sepsis Definitions Conference of 2001 guidelines [18,19];
- b) Experienced acute cognitive or neurological dysfunction during the course of septicemia while in the ICU;
- c) Received care in the ICU for longer than 72 hours;
- d) Received at least one head CT or brain MRI during ICU stay following the development of SAE; and

- e) Between ages 18 and 79 (inclusive).

The decision to perform brain imaging was based on the judgment of clinicians caring for the patient.

Patients with current or previous medical conditions (e.g., cardiac arrest) or treatments (e.g., chemotherapy) known to affect the structure or function central nervous system were excluded. Individuals 80 years of age or older were excluded due to an elevated risk of pre-ICU dementia or cerebrovascular disease. Severe sepsis was defined as sepsis associated with organ dysfunction. Septic shock was defined as the presence of sepsis with refractory arterial hypotension necessitating catecholamine infusion [7].

Sepsis-Associated Encephalopathy

SAE was defined as the development of one or more of the following conditions demonstrating acute central nervous system dysfunction concurrently with the onset of infection or during the course of sepsis:

- A. Acutely altered mental status,
- B. New-onset focal neurologic finding(s), or
- C. New-onset seizure [4,20,21].

Acutely altered mental status was defined as the development of coma, delirium, prolonged disorientation, misinterpretation of stimuli, hallucinations, delusions, or a change in sensorium [4]. *Focal neurologic deficit* was defined as any acute development of abnormalities on a neurological exam suggestive of brain, nerve, or spinal cord dysfunction. *Seizure* was defined as the transient occurrence of abnormal generalized tonic-clonic or recurrent focal motor or sensory abnormalities as observed and documented by a physician or nurse [22].

Each of these conditions were categorized as SAE if they were

1. Not previously documented in the patient's history prior to the ICU admission, and
2. Judged to have developed concomitantly with or following the onset of sepsis. Neurological exams, which consisted of an assessment of level of consciousness and arousal, orientation, speech, and ability to follow motor commands, were conducted approximately every four hours for all patients per standard-of-care. The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) [28] was used to assess delirium in 60% of patients. A validated chart-based method for identification of delirium [24] was used for patients without available CAM-ICU data.

Physiological Data

The Acute Physiology and Chronic Health Evaluation III (APACHE-III) [25] and Sequential Organ Failure Assessment (SOFA) [26] rating scales were used to quantify severity of systemic illness and organ dysfunction, respectively. The Charlson Comorbidity Index (CCI) was used to quantify the level of medical comorbidity [27]. A *cardiovascular health score* was generated by summing the weighted score of a subset of the CCI indices (i.e., myocardial

infarction, congestive heart failure, peripheral vascular disease or bypass, hypertension, use of coagulation therapy, and diabetes).

Neuroimaging

CT Imaging Protocol. Non-contrast CT (NCCT) of the head was performed on a 64-slice multi detector scanner (General Electric Medical Systems, Milwaukee, WI) according to routine departmental protocol utilizing contiguous 5.0 mm axial sections from the foramen magnum to the vertex without the intravenous administration of contrast. Standardized scanner parameters were set at 120 kVp, 200 mA, and 1 sec rotation time. **MR Imaging Protocol.** Non-contrast MR imaging of the head was performed on a 1.5T or 3.0T scanner (General Electric Medical Systems) according to routine scanning protocol utilizing sagittal T1-weighted image (WI), axial T1W, T2W, FLAIR, susceptibility and/or gradient echo, and diffusion-weighted imaging.

Two board certified radiologists with Certificates of Added Qualification (CAQ) in neuroradiology and over 15 years of experience reviewed all neuroimaging using a standardized rating form. Independent assessments of the CT or MR imaging examinations were performed blinded to the patient's clinical, treatment, and outcomes data. For patients who underwent multiple neuroimaging studies, only the first MRI and/or CT scans following the SAE event were rated. Nineteen scans were rated by both radiologists. The degree of agreement between raters ranged from "good" to "excellent" across all neuroimaging attributes (kappa scores: .68 - .89).

Patient MRI and CT scans were recorded as 'normal' and 'abnormal.' Brain atrophy was qualitatively graded as absent, mild, moderate, and severe. MRI and CT scans were also examined for the presence of lacunar infarction, petechial hemorrhage, gross

hemorrhage, encephalomalacia, arterial/venous calcification, and cerebral edema. All edema was categorized as either cytotoxic or vasogenic in origin and categorized as generalized versus focal. The neuroanatomical location and number of each neuroimaging abnormality were recorded. Periventricular and deep subcortical white matter lesion burden was rated as absent, mild, moderate, and severe using the Fazekas scoring method [28], a visual rating system designed for use with MRI and CT scans. Cerebral infarction, gross hemorrhage, petechial hemorrhage, and cerebral edema were classified as either acute or non-acute.

Statistical analysis

Analyses were performed using Stata SE Version 14 (StataCorp, College Station, Texas). Comparisons of patient groups on demographic, medical, and treatment-related variables were conducted using chi-squared/Fisher's exact test and Mann-Whitney U tests for categorical and continuous variables, respectively. Associations between SAE characteristics and neuroimaging attributes were evaluated using one-way between-group ANOVAs and chi-square tests. Multivariable adjusted logistic regression and Cox regression analyses were used to assess the association between acute and chronic neuroimaging findings, and ICU mortality, hospital discharge disposition, and one-year mortality. Covariates for logistic and Cox regression analyses included: age, sex, disease severity (day 1 APACHE-III), and cardiovascular disease (cardiovascular health score). All analyses were initially conducted using aggregated data from MRI and CT scans. To account for potential differences related to imaging modality, planned sensitivity analyses were also conducted using only data from CT imaging. Because of limited sample size, sensitivity analyses using only MRI data were not performed. All tests were two-sided, and $p < .05$ was considered statistically significant.

Results

Patient demographic and clinical data

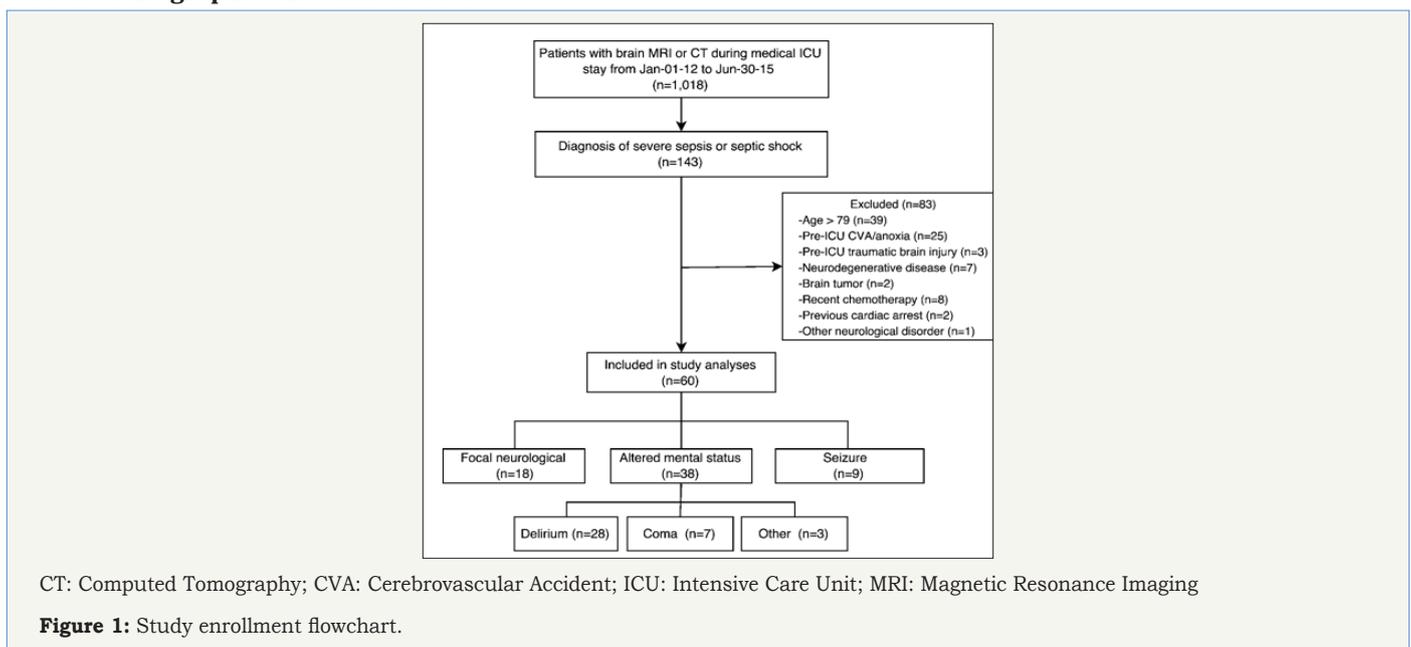


Figure 1: Study enrollment flowchart.

Table 1: Sample demographic, medical, and treatment-related characteristics stratified according to the presence of acute neuroimaging findings and level of white matter lesion burden.

Characteristic	Acute Imaging Findings (n = 13)	No Acute Imaging Findings (n = 47)	p	Moderate or Severe WM Lesions (n = 19)	Absent or Mild WM Lesions (n = 41)	p
Age – years	66 (52-75)	67 (62-74)	.82	73 (67-76)	65 (54-72)	.004
Caucasian race – n (%)	8 (62)	23 (49)	.99	8 (67)	23 (74)	.62
Male sex – n (%)	8 (62)	29 (62)	.96	15 (79)	22 (54)	.06
ICU Length of Stay – days	6 (5-15)	9 (5-17)	.58	8 (4-18)	9 (5-17)	.54
Hospital Length of Stay – days	12 (7-36)	22 (11-46)	.16	15 (9-33)	23 (9-47)	.38
ICU Days Before CT/MRI	4 (1-6)	3 (1-9)	.44	4 (1-9)	3 (1-9)	.62
APACHE III score, ICU day 1	90 (72-110)	90 (90-108)	.94	85 (72-93)	91 (72-116)	.37
SOFA, ICU day 1 (0 to 24)	8 (6-11)	8 (6-11)	.96	7(5-10)	8 (6-11)	.58
SOFA, ICU day 3 (0 to 24)	9 (5-9)	7 (4-11)	.74	7 (4-10)	7 (5-11)	.77
Charlson Comorbidity Index	4 (3-6)	4 (4-8)	.42	5 (4-8)	5 (4-7)	.73
Critical Illness – n (%)						
Severe sepsis	2 (15)	12 (26)	.52	5 (26)	8 (20)	.55
Septic shock	11 (85)	35 (75)	.52	14 (74)	33 (80)	.55
Cardiac	3 (23)	7 (15)	.48	4 (21)	6 (15)	.54
Respiratory distress / failure	8 (62)	26 (55)	.69	11 (58)	23 (56)	.90
Acute kidney injury	4 (31)	20 (42)	.44	6 (32)	18 (44)	.37
Acute liver failure	1 (8)	2 (4)	.62	0 (0)	3 (7)	.23
Multiple organ dysfunction	5 (39)	15 (32)	.66	5 (26)	15 (37)	.43
Co-morbid Conditions – n (%)						
Cardiac	4 (31)	16 (34)	.83	10 (53)	10 (24)	.03
Pulmonary	2 (15)	13 (28)	.37	7 (37)	8 (20)	.15
Kidney disease	5 (39)	22 (47)	.59	5 (26)	22 (54)	.05
Liver disease	1 (8)	5 (11)	.75	1 (5)	5 (12)	.41
Diabetes	8 (62)	23 (49)	.42	13 (68)	18 (44)	.08
Cancer	1 (10)	11 (23)	.21	3 (16)	9 (22)	.58
Cardiovascular health score	2 (2-4)	2 (2-4)	.97	3 (2-5)	2 (1-3)	.023
Mechanical ventilation						
Number of patients (%)	11 (85)	37 (79)	.64	16 (84)	32 (78)	.58

Number of days	4 (3-9)	7 (2-17)	.22	5 (2-14)	6 (2-16)	.56
Delirium						
Number of patients (%)	8 (62)	32 (68)	.69	14(73)	26 (63)	.43
Number of days	2 (2-7)	3 (3-5)	.99	3 (1-5)	2 (0-5)	.73
Sedation days	5 (1-9)	7 (3-13)	.35	6 (3-14)	7 (2-11)	.86

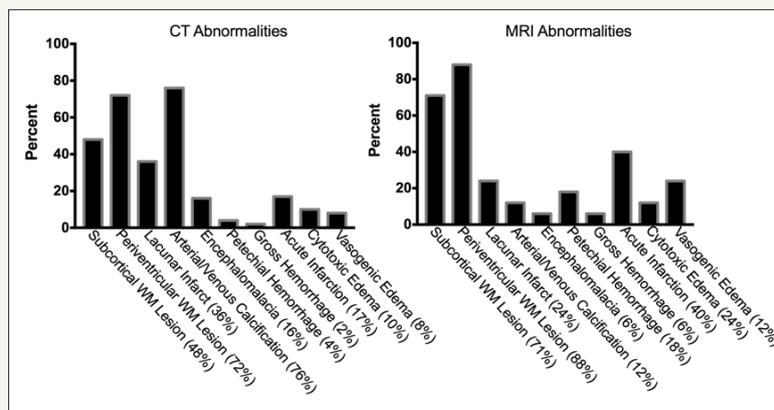
APACHE: Acute Physiology and Chronic Health Evaluation – Third Edition; SOFA: Sequential Organ Failure Assessment

Notes: Descriptive data are provided in the form of median followed by (interquartile range; IQR) unless otherwise specified. Patients with Fazekas scores > 3 were classified as having moderate to severe white matter lesion burden. χ^2 /Fisher’s exact test and the Mann-Whitney *U* were used to compare groups on categorical and continuous variables, respectively.

Between January 1, 2012, and June30, 2015, 60 patients were identified for inclusion (Figure 1). Patient demographic and clinical characteristics are presented in Table 1. The prevalence of SAE clinical features is described in Figure 1. Eight percent (5/60) of patients displayed more than one form of SAE before neuroimaging, and 27% (16/60) developed more than one form of SAE during the entirety of the ICU admission. The median number of days between ICU admission and identification of SAE was 2 for patients presenting with *acutely altered mental status* and seizure, and 3for patients presenting with a focal neurologic sign. Patients were in the ICU for a median of 3 days before receiving neuroimaging. No adverse events were reported during the transport to or from the radiological suite or during imaging.

Neuroimaging Findings

Eighty-three percent (50/60) of patients received one or more head CT;28% (17/60) received one or more MRI; 12% (7/60) received both a CT and an MRI. The prevalence rates of specific neuroimaging findings are displayed in Figure 2. Abnormal findings were present in 82% (49/60) of patients. Cerebral atrophy was present in 75% (45/60) of patients. Among patients with cerebral atrophy, severity ranged from mild (66%, 30/45) to moderate (33%, 15/45). Subcortical lesions, periventricular lesions, and arterial and venous calcification were most common in the frontal lobe. Lacunar infarcts were most common in the basal ganglia.



WM: White Matter

Figure 2: The prevalence of neuroimaging abnormalities among patients in the acute phase of sepsis-associated encephalopathy.

Acute neuroimaging findings were present in 22%(13/60) of patients. Among 11patients with acute infarction or hemorrhage, only three (27%) demonstrated evidence of new-onset focal neurological findings. Acute infarctions were unilateral in the majority of cases (73%, 8/11), and found most commonly in the frontal (55%, 6/11) and parietal lobes (36%, 4/11). Vasogenic edema was most common in the frontal (100%, 6/6)and temporal lobes (67%, 4/6). Cytotoxic edema was found at similar rates in the frontal (50%, 4/8), occipital (50%, 4/8), and parietal lobes(38%, 3/8). Edema was typically focal (80%-100%) and strongly associated with the presence of an acute infarction or hemorrhage ($\chi^2 = 13.66, p <.001$). Patients with acute neuroimaging findings

did not differ from those without acute findings on demographic, medical, and treatment-related variables (Table 1).

Seventy-seven percent (46/60) of patients demonstrated white matter lesions on neuroimaging. Compared to patients with mild or absent white matter lesion burden (Fazekas score ≤ 3), patients with moderate to severe white matter lesion burden were older (Mann-Whitney *U* = 209.00, *p* = .004), more likely to have comorbid cardiac disease ($\chi^2 = 4.66, p <.03$), and had a greater cardiovascular risk profile (Mann-Whitney *U* = 249.50, *p* = .023) (Table 1).

When patients were categorized according to the presenting clinical features of SAE and compared on neuroimaging attributes,

patient groups differed in regards to the level of cerebral atrophy ($F[2,57] = 3.78, p = .029$) and subcortical white matter lesion burden ($F[2,57] = 4.95, p = .010$), but did not differ on other neuroimaging attributes. Follow-up univariate analyses revealed that patients who presented with *acutely altered mental status* had greater levels of cortical atrophy and greater subcortical white matter lesion burden relative to patients who presented with focal neurologic deficits or seizures ($p < .05$).

Neuroimaging predictors of patient outcome

ICU mortality for the current sample was 17% (10/60), and one-year mortality was 40% (24/60). In a logistic regression model that adjusted for potential confounders (i.e., age, sex, APACHE-3

disease severity, and cardiovascular disease), the presence of an acute neuroimaging abnormality (i.e., infarction, hemorrhage, or edema) was associated with increased risk for ICU mortality (OR, 5.82, 95% CI, 1.23 to 27.56, $p = .026$). In a covariate-adjusted Cox regression model, the presence of an acute neuroimaging abnormality was also associated with increased risk for one-year mortality following ICU discharge (HR, 3.09, 95% CI, 1.23 to 7.72, $p = .016$). Kaplan-Meier survival curves are displayed in Figure 3. By comparison, total white matter lesion burden was not associated with either ICU mortality or one-year mortality. The relationships between neuroimaging attributes, ICU mortality, and one-year mortality were unchanged in sensitivity analyses that included only data from CT imaging (Table 2).

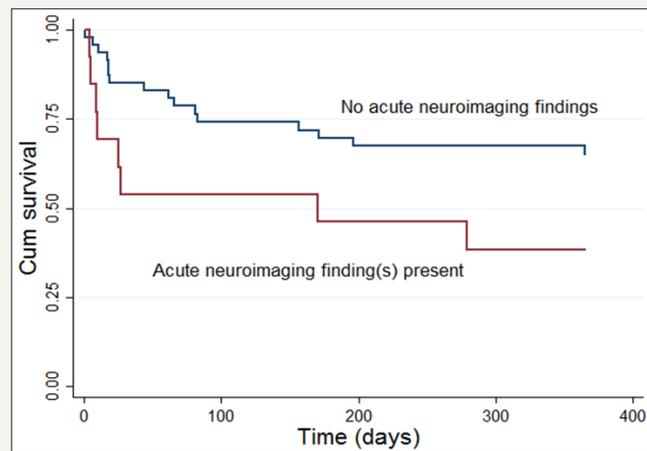


Figure 3: Kaplan-Meier survival curves evaluating the time to death in days for patients with and without acute neuroimaging abnormalities on MRI and/or CT scan following the onset of sepsis-associated encephalopathy ($p = .042$ by log rank test).

Table 2: Associations between neuroimaging variables and ICU mortality, one-year mortality, and disability at hospital discharge

Neuroimaging Variables	ICU Mortality OR (95% CI)	One-Year Mortality HR (95% CI)	Disability OR (95% CI)
Acute Neuroimaging Abnormalities (CT & MRI)	5.82 (1.23 -27.56)*	3.09 (1.23-7.72)*	6.52 (1.17-36.23)*
Acute Neuroimaging Abnormalities (CT only)	7.28 (1.26 -41.85)*	4.28 (1.51-12.14)**	6.55 (.69-62.39)t
Moderate to Severe White Matter Lesions (CT & MRI)	2.67 (.47-15.12)	1.45 (.58-3.63)	1.58 (.42-5.93)
Moderate to Severe White Matter Lesions (CT only)	1.58 (.14-23.73)	1.62 (.59-4.46)	.91 (.19-4.21)

[†] $p < .10$; * $p < .05$; ** $p < .01$

Notes: All models are adjusted for age, sex, cardiovascular disease, and day 1 disease severity (APACHE-III score). CI: Confidence Interval; HR: Hazard Ratio; OR: Odds Ratio

Of the patients discharged from the hospital, 64% (25/39) were discharged home (i.e., routine discharge) and 36% (14/39) required continued comprehensive medical and rehabilitation services. In a covariate-adjusted logistic regression model, the presence of an acute neuroimaging abnormality was independently associated with an increased need for comprehensive medical and rehabilitation services following hospital discharge (OR, 6.52, 95% CI, 1.17-36.23 $p = .032$). The association between acute neuroimaging findings and disposition at discharge did not change in a sensitivity analysis that included only data from CT imaging.

No association was found between white matter lesion burden and discharge disposition.

Discussion

In this study, we demonstrated that periventricular and subcortical white matter lesions, cerebral atrophy, and cerebrovascular calcification are the most common neuroimaging findings in patients with SAE, whereas acute neuroimaging findings, such as infarction and edema, are only found in a quarter of patients. Patients who developed *acutely altered mental status*

were found to have more severe cortical atrophy and greater white matter lesion burden relative to patients who developed other forms of SAE. However, no specific neuroimaging finding was associated with the development of new-onset focal neurologic signs or seizure. Additionally, we demonstrated that the presence of acute, but not chronic, neuroimaging findings during the course of SAE is associated with increased risk for ICU mortality, greater disability at the time of hospital discharge, and reduced survival during the subsequent year.

The only previous study to examine neuroimaging abnormalities in a large series of patients with SAE found evidence of ischemic stroke in 29% of patients, approximately double that of the present study (15%) [5]. Whereas the current study explicitly differentiated between acute infarctions and chronic lesions, it is unclear whether the ischemic strokes identified in this prior study represent acute infarctions, chronic silent infarctions, or both. Additionally, differences in stroke detection maybe due, in part, to differences in scan technique and/or imaging modality. The percentages of patients with severe periventricular (12%) and subcortical (17%) white matter abnormalities in the current study are similar to that which has been reported previously [5].

Given the age and prevalence of cardiovascular disease within our sample, it is likely that the white matter lesions and cerebral atrophy observed on neuroimaging predate the onset of sepsis [29]. However, in a previous study of ICU patients with acute neurologic changes (only 28% of whom were septic), the prevalence of white matter lesions and cerebral atrophy was 30% and 41%, respectively [30], compared to 77% and 75%, respectively, in the current study. Given these discrepancies, it is possible that the comparatively higher rates of white matter abnormalities and cerebral atrophy found in the current study are due to neuropathological processes unique to sepsis [8]. Whereas fluid redistribution, steroid use, and hypoxic ischemia have each been proposed as potential causes of rapid cerebral atrophy, blood-brain barrier dysfunction, reduced cerebral perfusion, and neurotoxic inflammatory mediators have each been identified as possible causes of white lesions in septic patients [15,16,31-36]. On the other hand, it is also possible that chronic white matter lesions and cerebral atrophy may predispose septic patients to developing SAE.

The ability to simultaneously examine a large number of potentially relevant neuroimaging biomarkers represents a strength of the current study. Although cerebral edema has been previously examined in a heterogeneous group of ICU patients [30], the present study is the first to assess the prevalence of cytotoxic and vasogenic edema in a large series of patients with SAE. Animal research and number of human case studies suggest that cerebral edema may occur commonly in patients with sepsis and SAE [9,37,38]. Similarly, previous literature also suggests that sepsis is a risk factor for posterior reversible encephalopathy syndrome (PRES), a neurotoxic state characterized by significant vasogenic edema [39]. However, the current results indicate that cytotoxic and vasogenic edema may only appear in 10% to 24% of patients with SAE, depending on the neuroimaging modality. The present

study is also the first to demonstrate high rates of cerebrovascular calcification among patients with SAE. Vascular calcification, a biological process marked by the deposition of calcium mineral deposits on intimal and medial layers of the vascular wall, is a common finding among middle-aged and older adults [40]. Vascular calcification can reduce arterial elasticity, contribute to atherosclerotic plaque burden, and in doing so, can promote inflammation and alter cerebral hemodynamics [41-43]. It is currently unclear whether cerebrovascular calcification increases one's risk for SAE.

The current results demonstrate that there is not necessarily a link between the clinical presentation of SAE and underlying neuroimaging abnormalities. Furthermore, our results suggest that neuroimaging abnormalities are not necessary for the development of SAE. However, the finding that only 33% of the patients with acute infarctions displayed focal neurologic signs underscores the importance of using neuroimaging for all forms of SAE [44]. Use of diffusion-weighted MRI (DWI) in patients with SAE may be especially helpful in the early identification of acute findings such as cytotoxic edema and acute infarction, which have prognostic significance as markers of disability and mortality [45].

Rates of mortality in the year following severe sepsis and septic shock are exceedingly high [2]. While it has been established that SAE is a risk factor for ICU mortality among patients with sepsis, the present study is the first to demonstrate that patients with SAE who develop acute neuroimaging abnormalities are at an elevated risk for mortality in the year following ICU discharge. In addition to highlighting the prognostic significance of acute neuroimaging findings among patients who develop SAE, the current results suggest that neurobiological processes related to SAE may directly influence survival of septic patients well after they leave the ICU. The exact nature of such a biological process remains unclear. However, mounting evidence suggests that cerebral infarction is associated with the depression of cell-mediated immune functioning [46,47], which may, in turn, increase susceptibility to infection [48,49] and subsequent mortality.

Limitations

The current findings should be interpreted within the context of several limitations, including a retrospective study design, a relatively small sample size, and a lack of baseline pre-critical illness neuroimaging. Larger prospective studies will be needed to confirm and extend the present results. Additionally, because only patients with overt SAE that necessitated neuroimaging for clinical purposes (as judged by a treating physician) were included in the study, patients with more subtle forms of SAE may have been overlooked. Similarly, there may be a subset of patients who were either too medically unstable to undergo a CT or MRI or who died before necessary neuroimaging could be performed. In general, CT scans are less sensitive than MR imaging for the detection of brain abnormalities [45]. Thus, the current study may have underestimated the true prevalence of acute and chronic neuroimaging findings. However, with the exception of

arterial and venous calcification, the prevalence of neuroimaging abnormalities did not differ significantly between patients with available MRI and patients with only CT imaging. Moreover, sensitivity analyses were used in the current study to confirm that CT imaging findings had similar prognostic significance to that of CT and MRI combined. The results of these sensitivity analyses are clinically relevant, as CT imaging is used more frequently than MRI to detect neurologic abnormalities in the acute medical ICU setting. Although neuroimaging is a powerful tool for the assessment of the pathological processes, many potential causes of SAE, including neurotransmitter abnormalities, microcirculatory and endothelial dysfunction, and changes in blood brain barrier permeability, are not directly observable using traditional structural imaging methods [9,20,32,50]. Future studies should make use of alternative imaging modalities capable of observing these neuropathological processes [16,51-53].

The multi-method approach to the assessment of delirium represents another limitation. Although the use of two distinct methods to assess delirium is not ideal, evidence suggests that the CAM-ICU and the chart-based delirium assessment method are highly comparable [23,24]. Lastly, more definitive conclusions about the pathophysiology of SAE could be reached if septic patients with and without SAE could be directly compared on the neuroimaging variables evaluated in the current study. However, given the life-threatening nature of critical illness, asking septic patients to undergo neuroimaging that is not clinically indicated may not be feasible.

Conclusion

Current findings suggest that SAE is a heterogeneous clinical syndrome that occurs early in the course of sepsis. Whereas chronic neuroimaging abnormalities such as cerebral atrophy, white matter lesions, and cerebrovascular calcification were found in the majority of patients, acute neuroimaging abnormalities, such as infarction, hemorrhage, and cerebral edema were less common. In general, neuroimaging findings do not necessarily correspond to specific clinical features of SAE. However, acute imaging finding, when present, are predictive of worse hospital outcomes and one-year mortality, highlighting the importance of neuroimaging for purposes of prognostication and clinical decision making. Future prospective multisite studies that implement more sensitive neuroimaging techniques will be especially helpful in corroborating our findings and furthering the understanding of the most common form of encephalopathy in the ICU.

Disclosure Statement

No potential conflict of interest was reported by the authors.

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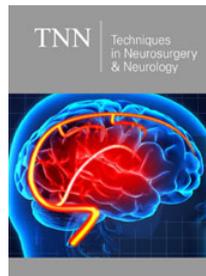
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