Independent risk factors associated with higher mortality rates and recurrence of brain abscesses from head and neck sources

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Objective. The aim of this study was to identify the features and independent risk factors associated with recurrence and mortality in patients with brain abscesses of head and neck origin.

Study Design. We designed a retrospective study of patients diagnosed with a brain abscess at the Massachusetts General Hospital between 1980 and 2017. Inclusion criteria were complete medical records, including medical and surgical history; and radiographic and microbiologic data. Multinomial logistic regression and Gray's test were used to evaluate the independent variables associated with recurrence and mortality.

Results. Eighty-eight cases met the inclusion criteria. Of these, 48 patients (54.5%) were men (mean age 50.5 ± 18.8 years). Significant association between etiology and cultured organisms was found only in cases of neurosurgical intervention with staphylococcal or streptococcal isolates ($P < .05$). Seizure activity was the only significant predictor of recurrence. Predictors of mortality included advanced age ($P = .005$); staphylococcal infection ($P = .029$); low monocyte count ($P = .004$); hyponatremia ($P = .002$); elevated blood urea nitrogen ($P = .000$); elevated creatinine ($P = .002$); hyperglycemia ($P = .023$); and status at discharge ($P = .000$).

Conclusions. Independent risk factors, such as low monocyte count, hyponatremia, renal dysfunction, and hyperglycemia, were found to be associated with higher mortality rates in patients with brain abscesses of head and neck origin. These abnormalities should be promptly recognized and aggressively treated. (Oral Surg Oral Med Oral Pathol Oral Radiol 2021;131:173−179)

A brain abscess is a focal or generalized intracerebral infection that can lead to headache, pyrexia, focal neurologic deficits, and ultimately death, if not treated promptly.[1,2] Brain abscesses usually occur as a result of contiguous spread from a local source of infection, such as the paranasal sinuses, or as a result of hematogenous dissemination from a distant infection, such as endocarditis.[3,4] Odontogenic infections are rarely considered causative.[5] The brain is relatively resistant to bacterial infection because of the blood−brain barrier and its rich blood supply but can be susceptible to infection after neurosurgical intervention.[6] The incidence of cerebral abscesses secondary to opportunistic infections in immunocompromised patients is also increasing.[7,8] The aims of treatment are to eliminate the infectious process through confined bony drainage and to avoid secondary cerebral injury.[1] Advances in neuroradiologic imaging techniques and antimicrobial therapy have helped reduce the reported mortality rates to less than 15% over the last few decades.[9] However, there are also conflicting reports of mortality rates as high as 35% during the same period.[6,10]

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The aims of this study are to analyze the clinical features of brain abscesses originating from head and neck sources treated at a tertiary care facility over a 30-year period and to determine what independent risk factors are associated with higher mortality rates and recurrence.

MATERIALS AND METHODS

Study design and study sample

This is a retrospective cohort study. The study population consisted of patients diagnosed with brain abscesses at the Massachusetts General Hospital between 1980 and 2017. Patients were identified by using the appropriate International Classification of Diseases 9th edition and International Classification of Diseases 10th edition coding for brain abscesses in the Massachusetts General Hospital Research Patient Database Registry. The inclusion criterion was diagnosis of a brain abscess, confirmed with both neuroimaging and positive microbiologic or histologic findings. Etiologic sources outside of the head and neck region resulted in exclusion of the case. Records were reviewed for the following: demographic data; clinical presentation; microbiologic data; laboratory values and neuroimaging findings; treatment; status at discharge;

Statement of Clinical Relevance

Independent risk factors, such as low monocyte count, hyponatremia, renal dysfunction, and hyperglycemia, were found to be associated with higher mortality rates in patients with brain abscesses of head and neck origin and, thus, deserve prompt recognition and aggressive treatment.

and outcomes and survival time. Institutional review board approval was obtained (Protocol 2018 P-000165), and the study was in compliance with the tenets of the Helsinki Declaration.

Data collection and analysis

Descriptive statistics (mean, frequency, range, and standard deviation) and multinomial logistic regression were evaluated by using SPSS version 19.0 (SPSS Inc., Chicago, IL). Variables with P values less than .1 in the univariate analyses were entered into a multivariate logistic regression model to identify independent predictors. Recurrence was the event of interest and death the competing risk. Cases with loss to follow-up or no recurrence or death were considered censored cases. The effects of the independent predictors on recurrence and mortality were evaluated by using Gray's test of competing risk analysis on R Software version i386 3.6.1 (Lucent Technologies, Inc., Murray Hill, NJ). P value less than .05 was considered statistically significant. The final figures were assembled by using CorelDRAW(R) Graphics Suite X4 (Corel, Ottawa, Ontario, Canada).

RESULTS

Demographic data and clinical presentation

In total, 167 patients with a diagnosis of brain abscess were identified from the data registry, as previously described.[11] Of these, 88 cases met the inclusion criteria and were evaluated. The mean age of the study patients was 50.5 (±18.8) years (range 7−90 years). There were 48 males (54.5%) and 40 females (45.5%). The most common etiology was paranasal sinusitis in 43 cases (48.9%), followed by neurosurgical intervention in 23 (26.1%), and odontogenic infection in 12 (13.6%). Sixty-one patients (69.3%) had a history of surgery, including neurosurgery and sinus surgery in 41 (46.6%) and oral/maxillofacial and neck surgery in 9 (10.2%). Smoking history was recorded in 27 (30.7%), alcohol use in 14 (15.9%), and drug abuse in 7 (8%). The most common presenting signs and symptoms included headache in 39 (44.3%) and pyrexia in 18 (20.5%). Specifics are summarized in Table I. There were no statistically significant associations between etiology and other factors, such as age, sex, past surgical history, cigarette use, alcohol use, drug abuse, and clinical presentation ($P > .05$).

Table I. Demographic data and clinical presentation

Parameters	*No. of patients (%)*
Demographic Characteristics	
Mean ± SD age (y)	50.5 ± 18.8 (7-90)
Sex (male/female)	48 (54.5)/40 (45.5)
Source of infection	
Sinus	43 (48.9)
Neurosurgical intervention	23 (26.1)
Odontogenic factor	12 (13.6)
Head trauma	6 (6.8)
Mastoid/ear	4 (4.5)
Past surgical history	
Neurosurgery and sinus surgery	41 (46.6)
Oromaxillofacial and neck region	9 (10.2)
Trauma history	11 (12.5)
Cigarette use	27 (30.7)
Alcohol use	14 (15.9)
Drug abuse	7 (8)
Clinical Presentation	
Headache	39 (44.3)
Pyrexia	18 (20.5)
Seizure	15 (17)
Neuromotor changes	15 (17)
Altered mental status	12 (13.6)
Neurosensory changes	12 (13.6)
Memory loss/cognitive impairment	10 (11.4)
Vomiting/nausea	9 (10.2)
Vertigo/dizziness	4 (4.5)
Fatigue	4 (4.5)

SD, standard deviation.

Microbiologic data

There were 66 cases (75%) of gram-positive infections, including 36 (40.9%) with *Staphylococcus*, 31 (35.2%) with *Streptococcus*, and 8 (9.1%) with *Peptostreptococcus*. There were 17 cases (19.3%) of gram-negative infections, including 6 (6.8%) with *Escherichia coli*, 3 (3.4%) with *Fusobacterium nucleatum* and 3 (3.4%) with *Haemophilus influenza*. Polymicrobial infections occurred in 23 patients (26.1%) and both gram-positive and gram-negative infections occurred in 13 patients (14.8%). In 3 cases (3.4%), fungal species were isolated. The microbiologic data are summarized in Table II. The only significant association between etiology and the microbiologic data was found in cases secondary to neurosurgical intervention, including head trauma, with isolates of *Staphylococcus* (estimated $\beta 1 = 2.197$; odds ratio = 9; $P = .011$) or *Streptococcus* (estimated $\beta 1 = -1.678$; odds ratio = .187; $P = .030$) identified (Figure 1). There were no statistical associations

Table II. Microbiology

Microorganism	*No. of patients (%)*
Gram-Positive Microorganisms	66 (75)
Staphylococci	36 (40.9)
Coagulase-negative *Staphylococcus*	20 (22.7)
Staphylococcus aureus	16 (18.2)
Streptococci	31 (35.2)
Streptococcus milleri	14 (15.9)
Streptococcus anginosus	7 (8.9)
Streptococcus pneumoniae	6 (6.8)
Streptococcus unspecified	4 (4.5)
Peptostreptococci	8 (9.1)
Gram-Negative Microorganisms	17 (19.3)
Escherichia coli	6 (6.8)
Fusobacterium nucleatum	3 (3.4)
Haemophilus influenza	3 (3.4)
Fungi	3 (3.4)

Suspected etiology	Microorganism	Estimated β1	Sig.	Exp(B)	95% CI of Exp(B) Min.	Max.
Neurosurgery	Staphylococci	2.197	0.011 *	9	1.672	48.437
Sinus/mastoid/ear	Staphylococci	1.076	0.194	2.933	0.578	14.885
Neurosurgery	Streptococci	-1.678	0.030 *	0.187	0.041	0.851
Sinus/mastoid/ear	Streptococci	-.020	0.974	0.98	0.285	3.37

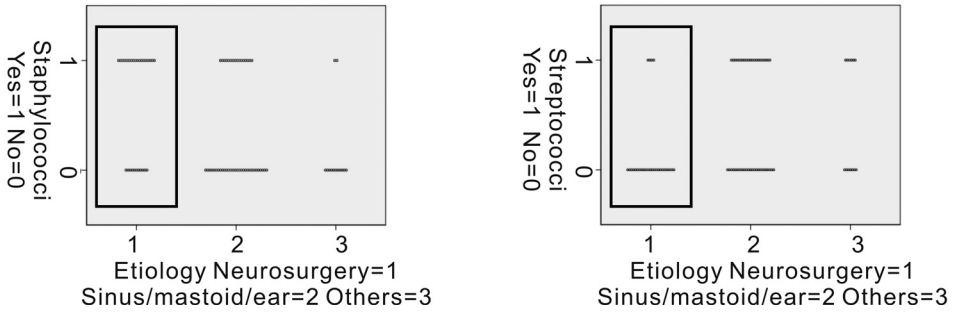

Fig. 1. The correlation between different microorganisms and etiology by multinomial logistic regression analysis. Black boxes indicate the positive or negative correlation; *, $P < .05$.

between microbiology and other factors, such as age, sex, past surgical history, cigarette use, alcohol use, drug abuse, and clinical presentation ($P > .05$).

Laboratory and neuroimaging findings

Computed tomography or magnetic resonance imaging was used to confirm the diagnosis.[12] Head computed tomography commonly demonstrated a rim-enhancing hypodense lesion in 1 or greater anatomic locations, with moderate surrounding edema and local mass effect consistent with an abscess. Magnetic resonance imaging commonly demonstrated a (multi-)lobulated, hyperintense central region and a hypointense peripheral ring,[13] surrounded by a thick, irregularly enhancing T2/fluid-attenuated inversion recovery signal abnormality consistent with an abscess. The right side of the brain was affected in 38 cases (43.2%) and the left side in 37 (42%). Bilateral involvement was found in 13 (14.8%). The frontal lobe was the most frequently affected site in 58 patients (65.9%), followed by the temporal lobe in 13 (14.8%). There were no statistically significant associations between the etiology and the site of infection, or between the microbiologic data and the site of infection ($P > .05$). The vital signs at presentation and the admitting laboratory values for the cohort are summarized in Table III.

Treatments and outcomes

All patients received antibiotic therapy. Seventy-nine cases (89.8%) were treated with surgical drainage, including 55 (62.5%) by open craniotomy, 17 (19.3%) by stereotactic drainage, and 7 (8%) by endoscopic

Table III. Laboratory and neuroimaging findings

Laboratory and radiologic findings	*No. of patients (%)/ mean ± SD*
Vital Signs	
Blood pressure (mm Hg)	127.5 (± 14.2)/ 69.9 (± 10.3)
Heart rate (beats/min)	87.6 ± 18.6
Respiratory rate (breaths/min)	18.5 ± 2.3
Temperature (°F)	99.7 ± 2.1
Hematology	
WBC (K/μL)	11.5 ± 5.6
HCT (%)	36.0 ± 5.1
Hgb (g/dL)	12.2 ± 1.9
PLT (K/μL)	293.7 ± 115.5
Multinucleated cells (%)	75.7 ± 13.0
Lymphocyte (%)	13.6 ± 8.3
Monocyte (%)	7.7 ± 5.2
Chemistry	
Sodium (mmol/L)	137.4 ± 4.8
Potassium (mmol/L)	3.8 ± 0.5
Chloride (mmol/L)	101.4 ± 6.1
Carbon dioxide (mmol/L)	25.4 ± 3.8
BUN (mg/dL)	14 ± 8
Creatinine (mg/dL)	0.9 ± 0.4
Blood glucose (mg/dL)	140.2 ± 60
Imaging	
Side(s)	
Right	38 (43.2)
Left	37 (42)
Both	13 (14.8)
Location	
Frontal	58 (65.9)
Temporal	13 (14.8)
Occipital	5 (5.7)
Others	12 (13.6)

BUN, blood urea nitrogen; *HCT*, hematocrit; *Hgb*, hemoglobin; *PLT*, platelet; *SD*, standard deviation; *WBC*, white blood cell.

Table IV. Treatments and outcomes

	No. of patients (%)
Treatments	
Antibiotic agents	88 (100)
Abscess drainage	80 (87.91)
Status at Discharge	
Improved/Stable	71 (80.7)
Clear/Normal	16 (18.2)
Deceased	1 (1.1)
Follow-Up	
Clear/Normal	51 (58)
Recurrence	18 (20.5)
Deceased	14 (15.9)
Lost	5 (5.9)

drainage through the paranasal sinuses. Seventy-one patients (80.7%) demonstrated improved or stable status at discharge. In 16 cases (18.2%), the infection was felt to be resolved at discharge. One (1.1%) patient succumbed to disease before discharge. Fifty-one patients (58.0%) presented with normal status at follow-up, 18 (20.5%) suffered from a recurrent brain abscess, and 13 patients (14.8%) died during follow-up. Five patients (5.7%) were lost to follow-up. Follow-up times varied greatly for individual patients. The 1-year and 5-year mortality rates at follow-up were 10.2% and 12.5%, respectively. Specifics are summarized in Table IV. However, there were no significant associations between outcomes and the following factors: treatment methods, age, sex, past surgical history, cigarette use, alcohol use, and drug abuse ($P > .05$).

Prognostic factors associated with recurrence and mortality

A higher recurrence rate was significantly associated with seizure activity, which was the presenting sign observed in 15 patients ($P = .041$). Statistically significant associations with higher mortality were found for the following independent predictors: advanced age (>55 years; $P = .005$); staphylococcal infection ($P = .029$); low absolute monocyte count (<4%; $P = .004$); hyponatremia (<135 mmol/L; $P = .002$); elevated blood urea nitrogen (BUN) (>25 mg/dL; $P = .000$); elevated creatinine (>1.5 mg/dL; $P = .002$); hyperglycemia (>110 mg/dL; $P = .023$); and status at discharge ($P = .000$). No mortality was reported in patients discharged with complete resolution. Specifics are summarized in Figure 2.

DISCUSSION

Brain abscesses are life-threatening neurologic infections, and yet there have been only limited studies on their etiology and independent predictors of recurrence and mortality. This study aimed to analyze cases of brain abscesses derived from a head and neck source, admitted and treated in a tertiary care hospital setting, and to identify predictors associated with recurrence and mortality.

In our cohort of 88 cases, the male-to-female ratio and mean age were consistent with those reported by other studies.[6,14] Bodilsen et al.[15] observed age (>40 years) as a significant risk factor for mortality in their cohort of 1384 cases. We identified advanced age (>55 years) as a significant predictor of increased mortality ($P = .005$).

Studies have identified the triad of headache, pyrexia, and altered mental status as the most common initial presenting symptoms in patients with brain abscesses.[1,6,16] In our study, 44.3% of patients (n = 39) presented with headache, 20.5% (n = 18) with pyrexia, and 13.6% (n = 12) with altered mental status. Our study also identified initial seizure presentation (15 cases [17%]) as the single most important predictor for disease recurrence ($P = .041$). This has not been reported previously.

The most commonly affected anatomic site in our cohort was the frontal lobe, as seen in 58 patients (65.9%), followed by the temporal lobe in 13 patients (14.8%). This is in agreement with the data presented by Roche et al.,[1] who observed frontal lobe as the most common site in a cohort of 163 patients. In a systematic review of 24 patients with intraventricular rupture of pyogenic brain abscesses, Omar et al. reported the temporal lobe to be the most common anatomic site.[14] No authors have reported a significant association between the anatomic site and mortality, and we were also unable to demonstrate any such association ($P > .05$).

The most common etiology of brain abscesses in the present study was pansinusitis, as seen in 43 patients (48.9%), followed by past neurosurgical intervention, as seen in 23 (26.1%). These results are also consistent with those reported in the existing literature.[1] Among neurosurgical interventions, those performed for penetrating brain injuries were reported to be one of the predisposing factors for abscesses development.[17] We identified a statistically significant association between etiology and dominant microorganisms in cases of neurosurgical interventions. Infections were positively associated with *Staphylococcus* ($P = .011$) and negatively associated with *Streptococcus* ($P = .030$). To our knowledge, this is the first study to report such an association.

We reported 66 cases (75%) of gram-positive infections and 17 cases (19.3%) of gram-negative infections. Staphylococci (40.9%) were the most commonly encountered microorganisms, followed by streptococci (35.2%). Similar results were reported by Prasad et al.[18] Our study observed a significant association between staphylococci and higher mortality rate ($P = .029$), which is in contrast to Tseng et al.,[9] who observed a favorable prognosis in infection with gram-positive cocci. Prasad et al.[18] observed gram-negative

Predictors	Status of follow-up	Stat.	Sig.	df
Age	Deceased	7.838	0.005 **	1
	Recurred	0.373	0.542	1
Staphylococci	Deceased	4.758	0.029 *	1
	Recurred	0.039	0.843	1
Seizure	Deceased	3.619	0.057	1
	Recurred	4.164	0.041 *	1
Monocyte	Deceased	8.093	0.004 **	1
	Recurred	0.057	0.811	1
Sodium	Deceased	9.593	0.002 **	1
	Recurred	1.077	0.299	1
BUN	Deceased	27.462	0.000 ***	1
	Recurred	1.014	0.314	1
Creatinine	Deceased	10.062	0.002 **	1
	Recurred	0.603	0.438	1
Glucose	Deceased	5.203	0.023 *	1
	Recurred	0.040	0.841	1
Status at discharge	Deceased	89.979	0.000 ***	2
	Recurred	-1	1	2

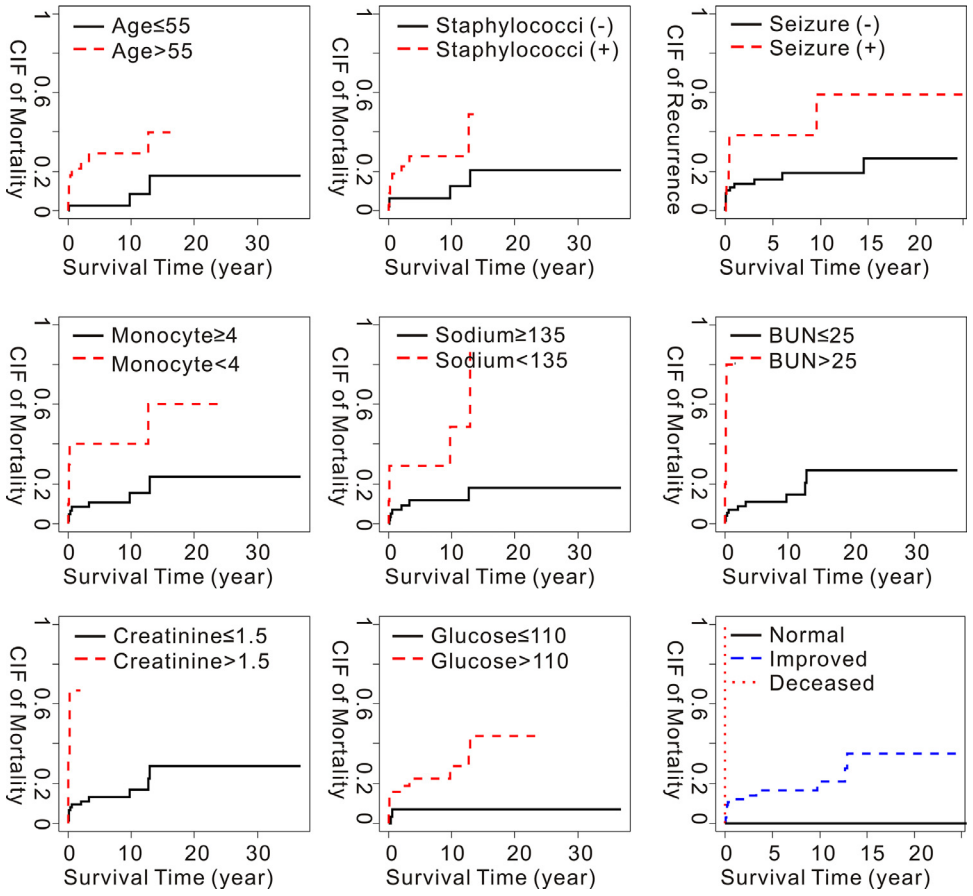

Fig. 2. The survival time and cumulative incidence functions (CIFs) between different predictors and the outcomes, determined by using Gray's test of competing risk analysis. *, $P < .05$; **, $P < .01$; ***, $P < .001$.

cultures to be significantly associated with mortality. Our study did not demonstrate this association. Further investigation is required to clarify these issues.

All study patients received antibiotic therapy, and 79 (89.8%) underwent surgical drainage, as described above. Although various authors have reported improved outcomes with intravenous antibiotics with or without surgical drainage,[19-21] we did not demonstrate any association between treatment modality and outcome. This is in agreement with Hakan et al. in their cohort of 96 patients.[22]

Our study is the first to address independent predictor variables associated with increased mortality and

recurrence in patients with brain abscesses. Longo et al. identified an elevated white blood cell count as a significant risk factor for recurrence.[23] Bodilsen et al. suggested that risk factors for death were advanced age (>40 years), presence of medical comorbidities, immunocompromise, and congenital heart disease.[15] In the present study, we found the following associations with increased mortality: low absolute monocyte count; hyponatremia; elevated BUN and creatinine; and hyperglycemia. We also observed a significant association between mortality rate and status at discharge ($P = .000$).

Hyponatremia (<135 nmol/L) was statistically associated with increased mortality in our cohort. Hyponatremia can be related, both physiologically and pathologically, to increased secretion of antidiuretic hormone, and its imbalance can reflect the severity of renal dysfunction.[24] In a cohort of 174 patients with hydrocephalus, van Gijn et al. observed increased mortality in those with hyponatremia,[25] likely as a result of increased brain edema causing brain herniation, respiratory failure, and death.

Elevated BUN (>25 mg/dL), a sensitive indicator of renal dysfunction, has been shown to be a predictor of mortality in patients with cardiac disease.[26,27] We also found this magnitude of BUN elevation correlated with increased patient mortality. Increased serum creatinine, an indicator of nephrotoxicity, has been associated with higher mortality in hospitalized patients,[28] and elevated creatinine (>1.5 mg/dL) was statistically significantly associated with mortality in our study.

Hyperglycemia can be a marker of disease severity and increased mortality, particularly in cases of sepsis. This likely reflects the massive release of cytokines and glucocorticosteroids commonly found in these infections.[29] In our cohort, hyperglycemia (>110 mg/dL) was associated with patient mortality.

Circulating monocytes are known to infiltrate infected sites, where they further differentiate into macrophages, to kill microbes and promote the repair of damaged tissue. Monocyte deficiency indicates deficiency in human leukocyte antigen−(HLA)-DR, a major histocompatibility complex II molecule. Low monocyte HLA-DR expression is a result of a compensatory host anti-inflammatory response. Excessive anti-inflammatory stimulation results in a state termed *immunoparalysis*.[30] Monocytopenia, an extreme form of monocyte deficiency, has been reported to be an independent risk factor for mortality secondary to an abnormal immune response.[31] It is associated with reduced circulating lymphocytes and natural killer cells, followed by a "cytokine storm." Resultant organ failure has been reported in such cases.[32] Our finding of an association between low absolute monocyte count (<4%) and mortality suggests the importance of HLA-DR expression.

The impact of these laboratory abnormalities on associated mortality in this patient population needs to be expediently recognized and the abnormalities aggressively treated in an effort to improve patient outcome. However, whether other independent risk factors, such as antimicrobial therapy, underlying medical problems/immune status of the patients, and the sizes of abscesses, are associated with recurrence and mortality, needs to be further studied.

CONCLUSIONS

The present study addressed the association between various risk factors and both recurrence and mortality in a cohort of 88 patients with brain abscesses originating from a head and neck source. Seizure activity was the only significant predictor of recurrence. Staphylococcal infection, low absolute monocyte count, hyponatremia, elevated BUN and creatinine, hyperglycemia, and patient status at discharge were initially found to have significant associations with mortality rates in patients with brain abscesses of head and neck origin. These abnormalities should be promptly recognized and aggressively treated.

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