



Predictors of Treatment Failure in Patients With Pyogenic Brain Abscess

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■ **BACKGROUND:** Pyogenic brain abscess poses a significant management challenge to clinicians, hence early diagnosis and interventions are critical. Our objective was to assess predictors of failure of therapy among patients with pyogenic brain abscesses according to surgical versus medical treatment.

■ **METHODS:** Retrospectively reviewed adults with pyogenic brain abscesses at our institution between 2009 and 2020. Treatment was classified as early surgical intervention and no early surgical treatment (medical therapy). Propensity score (PS) adjustment and multivariable regression were used to assess risk of treatment failure from surgical intervention and baseline covariates.

■ **RESULTS:** A total of 224 patients had pyogenic brain abscess, of whom 106 (47.3%) had early surgical treatment and 118 (52.7%) had medical treatment only. Significant predictors of surgical (vs. medical) treatment included essential hypertension (odds ratio [OR] 95% confidence interval [95% CI] = 2.06 [1.01–4.18]), abscesses number (single vs. multiple, OR [95% CI] = 4.81 [1.64–14.08]), midline shift (OR [95% CI] = 3.09 [1.22–7.82]). At 6 months, treatment failure cumulative incidence was 27.1% in the medical group (n = 31) and 21.3% in early surgical group (n = 22). PS-adjusted analysis showed beneficial effect of early surgical treatment (hazard ratio [HR] [95% CI] = 0.55 [0.31–0.98]). Multivariable regression showed similar but statistically nonsignificant estimate of surgical benefit (HR [95% CI] = 0.59 [0.34–1.01]; $P = 0.056$), and significant

associations of Charlson Comorbidity Index (CCI) ($P = 0.019$) and pre-existing central nervous system hardware ($P = 0.034$) with increased risk of treatment failure.

■ **CONCLUSIONS:** Higher CCI and pre-existing CNS hardware were significant risk factors associated with treatment failure. In propensity-adjusted analysis, early surgery was associated with a 45% reduction in risk of 6-month treatment failure.

INTRODUCTION

Pyogenic brain abscess poses a significant management challenge to clinicians. Despite its low incidence,¹ it is one of the most serious head and neck infection syndromes. Brain abscesses are associated with substantial morbidity and short- and long-term mortality.² Our understanding of the factors associated with treatment failure that correlate with poorer clinical outcomes in patients with brain abscesses remains limited, however.^{3,4}

In the present investigation, we aimed to profile characteristics of patients presenting with pyogenic brain abscesses and assess outcomes according to early surgical versus medical treatment alone while adjusting for the propensity to receive surgery.

METHODS

We retrospectively screened all cases of brain abscess seen at our institution from January 1, 2009, through June 30, 2020, to identify

Key words

- Brain abscess
- Bacterial
- Management
- Outcomes
- Predictors

Abbreviations and Acronyms

- CCI: Charlson Comorbidity Index
CI: Confidence interval
CNS: Central nervous system
HR: Hazard ratio
IQR: Interquartile range
OR: Odds ratio
PS: Propensity score

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all adult (≥ 18 years of age) patients with monomicrobial bacterial brain abscess. Electronic health records were reviewed. All patients had consented to use of their medical records for research purposes, and the institutional review board approved the study proposal.

Case definitions and variables included in this database were defined using criteria previously described by our research team.⁵ We defined brain abscess as a localized intracerebral collection of necrotic material surrounded by a well-vascularized capsule visible on imaging with either a cranial computed tomography scan or magnetic resonance imaging.⁶ We excluded polymicrobial infections and those caused by mycobacteria, nocardia, fungi, or parasites. Types of pre-existing central nervous system (CNS) hardware included metal plates, ventriculoperitoneal shunts, leads, and electrodes.

For purposes of treatment comparison, patients were classified into 2 groups according to those who underwent “early” surgical treatment, as defined below, and those who underwent medical therapy alone; all patients without “early” surgery were assigned to the medical group regardless of subsequent surgical treatment. *Medical management* was defined as the use of empiric or targeted antibiotic therapy for the treatment of brain abscess, which might be considered in specific cases, including deep-seated infection not amenable to surgery, small or multiple abscesses, or coexisting meningitis.⁷ *Early surgical treatment* was defined as therapeutic surgery that occurred within 1 week (7 days) of the initial diagnosis of brain abscess. *Surgical management* was defined as a therapeutic surgical intervention involving a surgical incision aimed at stereotactic drainage of an abscess or craniotomy with complete abscess removal. Additionally, to enable comparisons defined by surgical treatment anytime during the follow-up period, we constructed a time-dependent variable in which surgical treatment status was updated daily up until 6 months. Of note, the patient group who received surgical treatment also received medical treatment (antibiotic therapy). *Therapeutic failure* was defined as a brain abscess size progression or the development of a new abscess within 6 months despite initial medical or early surgical therapy. Accordingly, treatment failure outcomes were compared between the 2 groups among event-free patients (no cause-related death or relapse) at 1-week follow-up.

Statistical Analysis

Descriptive statistics on baseline data are reported as median (interquartile range [IQR]) or number (percentage), as appropriate. For the primary treatment comparison, patients were classified into 2 treatment groups based on whether surgical intervention occurred within 1 week of diagnosis; patients who failed earlier than 1 week were excluded. Propensity score (PS) adjustment was used to control for confounding captured by modeling the tendencies for treatment selection. Estimation of PS was based on a multivariable logistic regression, from which the predicted probability of receiving early surgical treatment was obtained as a function of 23 patient baseline descriptors. To support the validity of this method, baseline covariate imbalances between the 2 treatment groups were examined before and after PS adjustment using, respectively, analysis of variance and analysis of covariance models for continuous variables or unadjusted and adjusted logistic models for categorical variables.

For the primary outcome comparison, the treatment effect was assessed after statistically adjusting for PS as a covariate in a Cox regression model for time to treatment failure up to 6 months. PS entered this analysis as logit-transformed scores that were expanded using 3-knot restricted cubic splines to allow for nonlinear effects. In addition, we performed a similar PS-adjusted analysis that considered the time to early treatment in a dose-response manner. Specifically, to test whether the early treatment effect varied according to how quickly surgery was performed after diagnosis (range 0–7 days), a semi-continuous dose-response scale was constructed based on the days since surgery at day 7 with an override for no early surgery (setting days to -1). This variable entered the Cox model with a quadratic term to allow for a nonlinear relationship with the outcome.

As a second adjusted analysis but using all available patients, risk of 6-month failure from treatment type and relevant covariates was assessed using an extended Cox regression model in which the indicator for surgical treatment (at any time during follow-up) was incorporated as a time-dependent variable. Covariates in the model were limited to a number the sample could support and were chosen a priori based on clinical relevance: age, Charlson Comorbidity Index (CCI), pre-existing CNS hardware, midline shift, and the number (single vs. multiple) and size of brain abscesses. Statistical analysis was performed using the programming language R, version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

This case series has been reported in line with the PROCESS Guideline.⁸

RESULTS

Demographic and Clinical Data

Overall, 228 patients with pyogenic brain abscesses were identified during the study period. **Figure 1** displays the cumulative incidence of patients receiving surgical treatment over the first 24 days from diagnosis. Utilization of surgery increased sharply early on, from 22.8% ($n = 52$) at day 0 (date of diagnosis) to 47.0% ($n = 107$) at day 7 but leveled off thereafter. Of the 121 patients who did not undergo early (7-day) surgery, only 18 subsequently received surgical intervention after a median of 17.0 (IQR 13.3–88.8) days. Overall, 4 patients died within the first week following diagnosis and were excluded from the primary treatment comparison. Of the remaining 224 patients, 106 (47.3%) had early surgical treatment, and 118 (52.7%) had medical treatment.

Demographic, underlying comorbid conditions, and radiographic characteristics for both groups are summarized in **Table 1**. There was no significant difference in age at presentation for both the medical and early surgical groups. Similarly, there was no difference in the prevalence of comorbid medical conditions and microbiologic characteristics between groups. A comparison of the medical and surgical baseline descriptors in unadjusted analyses revealed some imbalances in radiographic details, including the number and size of abscesses and presence of a midline shift. However, none of the baseline differences persisted after PS adjustment, demonstrating adequacy of this technique in balancing covariates between treatment groups. Of note, a total of 20 (9%) patients reported ventriculitis on presentation. Twenty-one (9%) patients had pre-existing CNS

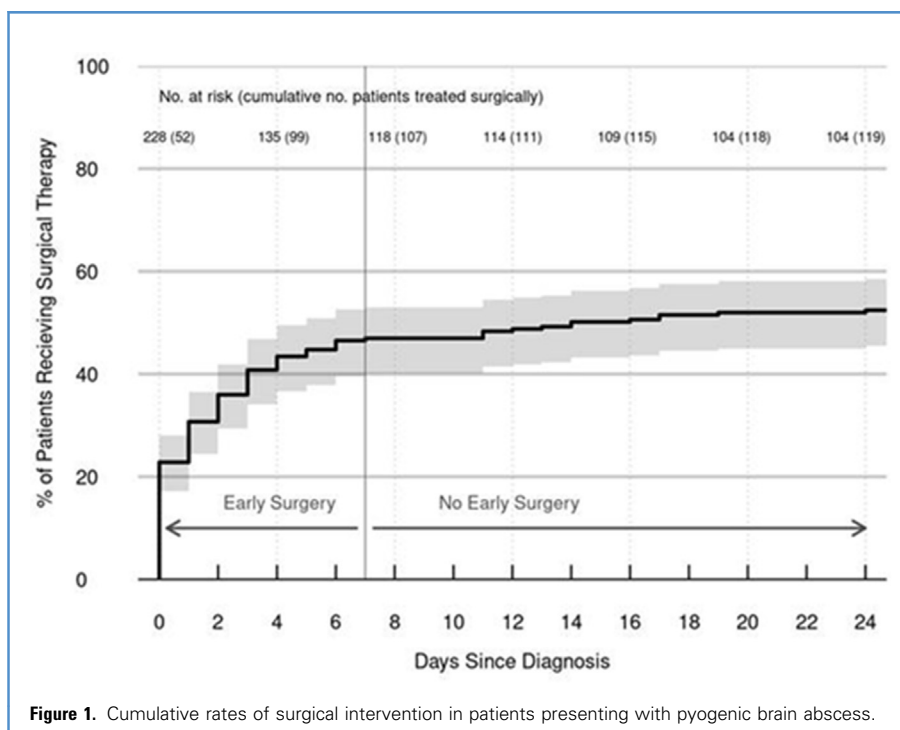


Figure 1. Cumulative rates of surgical intervention in patients presenting with pyogenic brain abscess.

hardware, with a mean of 1068 days from hardware implantation to brain abscess diagnosis, likely excluding these as postoperative infections.

Predictors of Treatment and Therapeutic Failure

Propensity analysis further allowed a multivariable examination of baseline factors that predicted the treatment received in patients presenting with pyogenic brain abscess. **Figure 2** displays the partial effects of all 23 propensity factors, ranked from least to most important. Significant predictors of early surgical (vs. medical) treatment included essential hypertension (odds ratio [OR] 95% confidence interval [CI] = 2.06 [1.01–4.18]; $P = 0.047$), single (vs. multiple) abscesses (OR [95% CI] = 4.81 [1.64–14.08]; $P = 0.004$), and the presence of midline shift (OR [95% CI] = 3.09 [1.22–7.82]; $P = 0.017$).

During the 6-month follow-up period, a total of 53 patients had treatment failure, including 31 in the medical group and 22 in the surgical group. The unadjusted 6-month cumulative rate of failure was 27% in the medical group and 21% in the early surgery group, with no significant difference between treatments ($P = 0.309$). After adjusting for PS, however, the differences between the 2 curves become more pronounced (**Figure 3**). Cox analysis demonstrated a significant PS-adjusted effect of early surgical treatment ($P = 0.042$), with an estimated hazard ratio (HR) of 0.55 (95% CI = [0.31–0.98]) indicating a 45% (95% CI = [2%–69%]) reduction in risk of treatment failure in patients who received early surgical treatment as compared to that in non-surgical patients (**Table 2**). In a separate propensity-adjusted Cox regression model, the dose–response relationship between time to early intervention and treatment failure was not statistically significant ($P = 0.114$),

suggesting that the specific timing of early treatment showed no incremental value beyond the type of early treatment.

The second adjusted analysis that included 6 covariates and incorporated treatment as a time-dependent variable showed a surgical benefit that was comparable in magnitude (hazard ratio [HR] [95% CI] = 0.59 [0.34–1.01]) but did not meet the conventional level of statistical significance ($P = 0.056$). In this multivariable model, a higher CCI ($P = 0.019$) and presence of pre-existing CNS hardware ($P = 0.034$) were significant risk factors associated with treatment failure, whereas presence of a midline shift ($P = 0.055$) and single abscess ($P = 0.087$) both trended toward significance (**Table 3**).

DISCUSSION

Our investigation is one of the largest to analyze risk factors associated with therapeutic failure in patients with pyogenic brain abscesses. The findings indicate that patients with essential hypertension, single brain abscess, and midline shift were more likely to undergo early surgical treatment for brain abscess, and that early surgical treatment was associated with lower risk of 6-month treatment failure after propensity adjustment. In multivariable analysis, a higher CCI and pre-existing CNS hardware were both independent predictors of therapeutic failure, regardless of medical or surgical management strategy. We believe our observation provides valuable prognostic information to patients and providers when making critical management decisions, such as need for early surgical intervention and patient counseling regarding prognosis.

Table 1. Comparison of Medical and Surgical Baseline Descriptors in Patients With Pyogenic Brain Abscess

Variable	Therapeutic Management (n = 224)		P Value	
	Medical (n = 118)	Early Surgical (n = 106)	Before PS Adjustment	After PS Adjustment
Demographic Characteristics				
Age at diagnosis of infection (y), median (IQR)	56.4 (45.7–65.7)	58.7 (47.2–65.9)	0.921§	0.865§
Male sex, n (%)	78 40 (66.1)	70 (66)	0.992	0.939
White race, n (%)	109 (92.4)	96 (90.6)	0.629	0.950
Comorbidities, n (%)				
Diabetes mellitus	28 (23.7)	27 (25.5)	0.762	0.933
Chronic kidney disease	20 (16.9)	22 (20.8)	0.467	0.935
Congestive heart failure	18 (15.3)	13 (12.3)	0.518	0.912
Malignancy	36 (30.5)	44 (41.5)	0.087	0.942
History of stroke	7 (5.9)	11 (10.4)	0.227	0.937
Immunosuppressive* or corticosteroid† therapy	27 (22.9)	17 (16.0)	0.200	0.944
Hypertension	28 (23.7)	36 (34.0)	0.092	0.943
Peripheral vascular disease	29 (24.6)	22 (20.8)	0.496	0.962
Charlson Comorbidity index, median (IQR)	5.0 (2.2–8.0)	5.0 (3.0–8.0)	0.870§	0.944§
Radiographic characteristics				
Size‡ (mm), median (IQR)	15.0 (10.0–28.8)	22.0 (13.0–30.0)	0.022 §	0.993§
Multiple‡, n (%)	29 (24.6)	7 (6.6)	<0.001	0.518
Midline shift, n (%)	10 (8.5)	24 (22.6)	0.004	0.471
Fluid collection location, n (%)				
Frontal lobe	54 (45.8)	53 (50.0)	0.526	0.907
Temporal lobe	30 (25.4)	26 (24.5)	0.877	0.995
Parietal lobe	35 (29.7)	25 (23.6)	0.306	0.950
Microorganisms				
<i>Staphylococcus aureus</i>	25 (21.2)	31 (29.2)	0.1661	0.961
Viridans group streptococci	24 (20.3)	24 (22.6)	0.6751	0.998

Bold indicates statistical significance.

IQR, interquartile range; PS, propensity score.

*Calcineurin inhibitors, anti-proliferative agents, mammalian target of rapamycin inhibitor, monoclonal antibodies.

†Prednisone (≥ 2.5 mg/day).

‡Abscess.

§Analysis of variance and analysis of covariance models.

||Unadjusted and adjusted logistic regression models.

Although some associations have been previously reported (albeit, in smaller cohorts of patients^{9–11}), we have identified novel predictors associated with choice of therapy and the development of treatment failure in patients with brain abscess. Essential hypertension likely played an important role regarding treatment selection. Patients with vascular pathologies have an increase in proinflammatory mediators that may cause complex molecular and ultrastructural damages. The combination of oxidative stress, increased cytokine levels, changes in blood–brain barrier permeability, and the injury to the brain's vascular endothelium

could eventually damage surrounding brain parenchyma.¹² Although essential hypertension was statistically significant in our study, perhaps it is not clinically and surgically significant in terms of treatment assignment or neurosurgical decisions. Likewise, a higher CCI was an independent risk factor associated with treatment failure. The CCI is a widely validated measure of the prognosis in numerous medical conditions, with significant relationships between the CCI and poorer outcomes in multiple diseases,^{13,14} and similar observations centered on brain abscess-associated mortality have been reported.^{11,15}

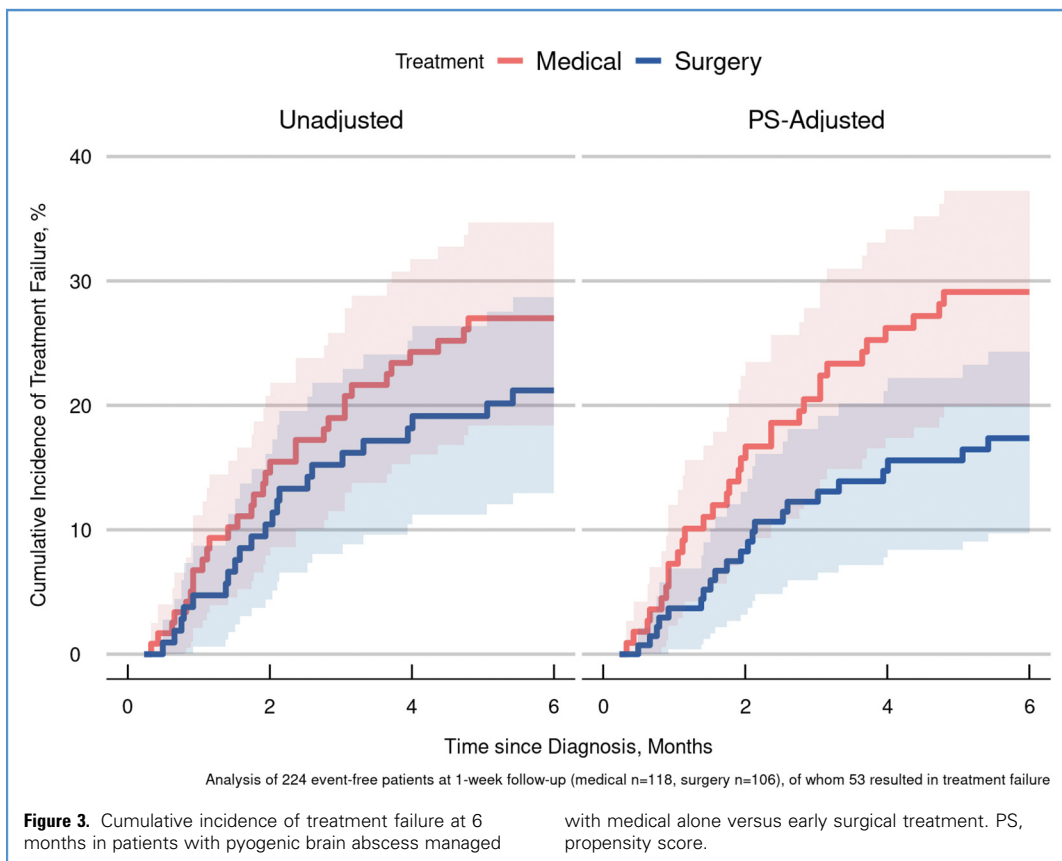
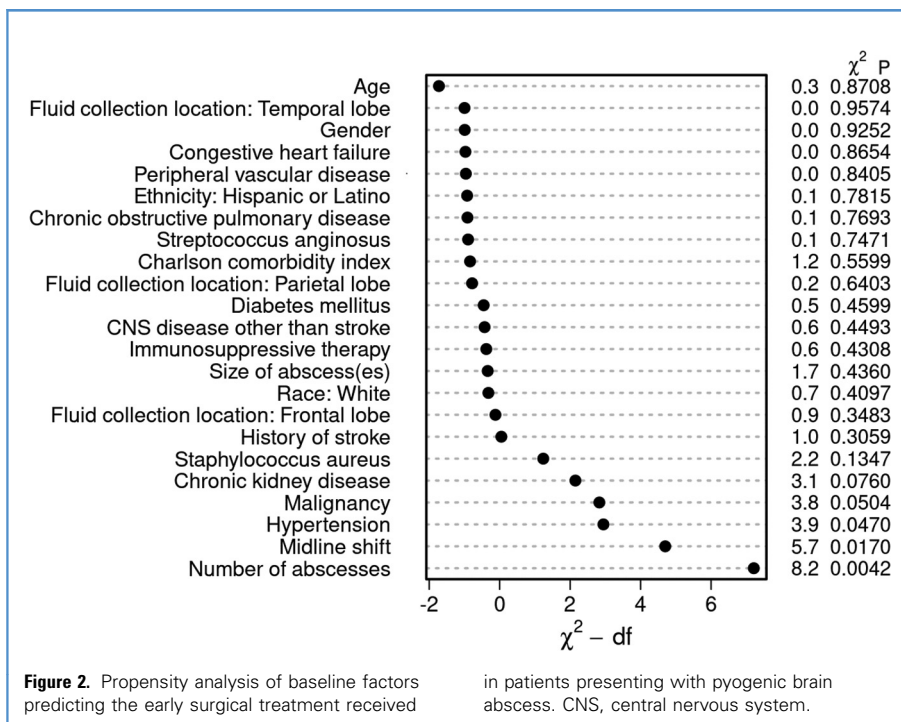


Table 2. Cox Analyses for Treatment Effect on 6-Month Failure in Patients With Pyogenic Brain Abscess

Treatment Effect	Model	Surgical: Medical HR (95% CI)	P Value
“Early” treatment (n = 224)*	Unadjusted	0.75 (0.44–1.30)	0.309
	PS-adjusted†	0.55 (0.31–0.98)	0.042
“Anytime” treatment (n = 228)‡	Multivariate-adjusted§	0.59 (0.34–1.01)	0.056

Bold indicates statistical significance.
 CI, confidence interval; HR, hazard ratio; PS, propensity score.
 *We defined “early” treatment as surgery/medical vs. medical therapy alone within the first 7 days of diagnosis and assessed its association with failure in a landmark analysis of 7-day survivors, with and without propensity score adjustment.
 †We created a time-dependent treatment variable that considered surgical therapy anytime within the 6-month follow-up period, and included this variable in an extended, multivariable Cox regression model.
 ‡Propensity scores were modeled with a restricted cubic spline in the logit values.
 §Model adjusted for age, Charlson index, midline shift, and the size and number of brain abscesses.

Hardware-associated CNS infections represent a significant subgroup of health care-associated infections.¹⁶ Microbial biofilm formation on prosthetic surfaces or devitalized tissue protects microorganisms from the host immune response and antimicrobial therapy. Pre-existing CNS hardware can serve as a nidus of infection,¹⁷ and, as demonstrated in our study, be a significant risk factor associated with treatment failure. A key difference from a spontaneous brain abscess is that if a patient has prior head surgery, more likely another surgery would be performed to remove the abscess and increase the chance of a better outcome.

Demir et al.¹⁸ in 2007 proposed an imaging severity index (ISI) score for brain abscess, which included the number, location, the largest diameter of the abscess, presence of surrounding edema, and midline shift. As an ISI score increases, the severity of an abscess escalates with a corresponding increase in neurological deficits and mortality. In our study, patients with single brain abscess and presence of midline shift were more likely to receive early surgical treatment, which was associated with improved outcomes at 6 months.

In our analysis, PS adjustment resulted in a 45% reduction in the risk of treatment failure for those who received early surgical treatment compared to that in nonsurgical cases. The choice of type, and most significantly, surgical procedure time, is often individualized for each patient, with no defined guidelines.

Antimicrobial therapy has traditionally been administered for 6–8 weeks in patients with bacterial brain abscess, and surgical therapy is frequently considered for therapeutic optimization or if the clinical condition is not improving within 2 weeks.¹⁹ Nevertheless, Lange et al. reported a mean length of 1.5 months (range 1–23 months) between initial brain abscess diagnosis and surgery.²⁰ Identifying patients with pyogenic brain abscess who may benefit from early surgical intervention is crucial. As time is a continuous variable, the earlier the intervention, the more beneficial to the outcome for the patient. At the same time, it is critical to recognize factors associated with therapeutic failure to counsel patients regarding the pro and cons of surgical intervention versus nonsurgical medical management. However, the choice between nonsurgical versus early surgical treatment must be used in a personalized fashion.²¹ Moreover, all patients with confirmed pyogenic brain abscess should be evaluated as soon as possible for early surgical intervention, regardless of clinical and radiologic presentation. This paper confirms that source control is especially critical in pyogenic abscess of the brain and is consistent with prior literature.

Limitations

Our study is retrospective, and this design has inherent limitations. A referral bias is a possibility considering the large tertiary

Table 3. Multivariable Cox Analysis of Risk Factors of 6-Month Treatment Failure on All Patients With Pyogenic Brain Abscess

Variable	Comparison	HR (95% CI)	P Value
Treatment	Surgical: Medical	0.59 (0.34–1.01)	0.056
Age	66.2 y: 46.1 y	1.26 (0.82–1.95)	0.288
Charlson Comorbidity Index	8 : 3	1.69 (1.09–2.61)	0.019
Pre-existing CNS hardware	Yes: No	2.21 (1.06–4.62)	0.034
Number of abscesses	Single: Multiple	2.30 (0.89–5.96)	0.087
Midline shift	Yes: No	1.94 (0.99–3.83)	0.055
Size of abscess	30 mm: 10 mm	1.00 (0.65–1.54)	0.998

Bold indicates statistical significance.
 CI, confidence interval; CNS, central nervous system; HR, hazard ratio.

academic nature of our practice. It is certainly possible that patients referred to our medical center were sicker and more likely to have received prior courses of antimicrobial therapy. This might influence our data, affecting the subsequent interpretation of results. Additionally, the relatively small number of treatment failures did not permit a thorough examination of risk factors nor the development of a robust scoring system to define predictors of therapeutic failure in these patients presenting with pyogenic brain abscess. Lastly, although we included a long list of 23 baseline descriptors in our PS model, any propensity analysis is susceptible to bias due to unmeasured covariates and thus we cannot exclude the possibility of residual confounding in our treatment comparison.

CONCLUSIONS

Compared with patients who did not undergo surgery, those who underwent early surgical intervention had a 45% reduction in risk

of treatment failure after adjusting for their propensity for being treated with surgery. In addition, a higher burden of comorbidities and pre-existing CNS hardware were independent risk factors associated with treatment failure. Our findings warrant further investigations in a larger cohort for validation.

CRedit AUTHORSHIP CONTRIBUTION STATEMENT

Cristina Corsini Campioli: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **John C. O'Horo:** Supervision, Writing – review & editing. **Brian D. Lahr:** Formal analysis, Methodology, Writing – review & editing. **Walter R. Wilson:** Supervision, Writing – review & editing. **Daniel C. DeSimone:** Writing – review & editing. **Larry M. Baddour:** Writing – review & editing. **Jamie J. Van Gompel:** Writing – review & editing. **M. Rizwan Sohail:** Visualization, Writing – review & editing.

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