

## Predictors of surgical site infection in glioblastoma patients undergoing craniotomy for tumor resection

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**OBJECTIVE** Surgical site infections (SSIs) burden patients and healthcare systems, often requiring additional intervention. The objective of this study was to identify the relationship between preoperative predictors inclusive of scalp incision type and postoperative SSI following glioblastoma resection.

**METHODS** The authors retrospectively reviewed cases of glioblastoma resection performed at their institution from December 2006 to December 2019 and noted preoperative demographic and clinical presentations, excluding patients missing these data. Preoperative nutritional indices were available for a subset of cases. Scalp incisions were categorized as linear/curvilinear, reverse question mark, trapdoor, or frontotemporal. Patients were dichotomized by SSI incidence. Multivariable logistic regression was used to determine predictors of SSI.

**RESULTS** A total of 911 cases of glioblastoma resection were identified, 30 (3.3%) of which demonstrated postoperative SSI. There were no significant differences in preoperative malnutrition or number of surgeries between SSI and non-SSI cases. The SSI cases had a significantly lower preoperative Karnofsky Performance Status (KPS) than the non-SSI cases (63.0 vs 75.1,  $p < 0.0001$ ), were more likely to have prior radiation history (43.3% vs 26.4%,  $p = 0.042$ ), and were more likely to have received steroids both preoperatively and postoperatively (83.3% vs 54.5%,  $p = 0.002$ ). Linear/curvilinear incisions were more common in non-SSI than in SSI cases (56.9% vs 30.0%,  $p = 0.004$ ). Trapdoor scalp incisions were more frequent in SSI than non-SSI cases (43.3% vs 24.2%,  $p = 0.012$ ). On multivariable analysis, a lower preoperative KPS (OR 1.04, 95% CI 1.02–1.06), a trapdoor scalp incision (OR 3.34, 95% CI 1.37–8.49), and combined preoperative and postoperative steroid administration (OR 3.52, 95% CI 1.41–10.7) were independently associated with an elevated risk of postoperative SSI.

**CONCLUSIONS** The study findings indicated that SSI risk following craniotomy for glioblastoma resection may be elevated in patients with a low preoperative KPS, a trapdoor scalp incision during surgery, and steroid treatment both preoperatively and postoperatively. These data may help guide future operative decision-making for these patients.

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**KEYWORDS** surgical site infection; craniotomy; glioblastoma; predictors; oncology; tumor

CARING for patients with glioblastoma (GBM) requires complex multidisciplinary care, often presenting unique challenges to both surgeons and patients.<sup>1,2</sup> The highly aggressive nature of these tumors necessitates maximally safe tumor resection followed by chemotherapy and radiation protocols, now considered the standard of care for GBM.<sup>1</sup> Postoperative recovery places an immense physical burden on patients, requiring careful and optimized care to minimize the occurrence of several postoperative complications. Among these complications,

surgical site infection (SSI) places significant stress on both patients and hospitals, in part because of increased medical costs, readmissions, reoperations, prolonged lengths of stay, and in some cases patient mortality.<sup>3–5</sup> Current estimates of postoperative SSI in cranial surgery range from 3.25% to 10%.<sup>6</sup> Within neurosurgical cases, GBM patients are considered among those with the highest risk for SSI given their likelihood of receiving chemotherapeutics that cause immunosuppression, radiotherapy, and repeat craniotomies for tumor resection.<sup>7</sup> Therefore,

**ABBREVIATIONS** AGR = albumin/globulin ratio; ASA = American Society of Anesthesiologists; GBM = glioblastoma; KPS = Karnofsky Performance Status; mFI-5 = 5-factor modified frailty index; NRI = nutritional risk index; PNI = prognostic nutritional index; SSI = surgical site infection.

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minimizing the risk of SSI in GBM patients presents an attractive opportunity to optimize their recovery following tumor resection and improve their ability to undergo further treatment.

Previous studies have assessed SSI risk factors in a variety of surgical settings; however, predictors of SSI risk following GBM resection have not been universally delineated.<sup>8,9</sup> Outlining potential predictors may be clinically useful to neurosurgical care teams and may aid in the upfront identification of at-risk patients, with an ultimate goal of patient-specific interventions to minimize SSI risk. Thus, we aimed to elucidate the effect of several demographic and clinical characteristics inclusive of scalp incision type on SSI risk following GBM resection.

## Methods

### Study Design

We retrospectively identified patients who had undergone craniotomy for GBM resection at our institution between December 2006 and December 2019. Preoperative clinical and demographic data were collected via manual chart review of anesthesia records, operative notes, radiological imaging, and preoperative laboratory tests. Lead surgeon experience was represented as the average years of practice since the completion of residency training, as similarly defined in prior studies.<sup>10,11</sup> The lead surgeon was the operating surgeon, and residents of varying postgraduate years were present to assist during the operation. Institutional policy requires the operating surgeon to be present during the critical portion of the case, inclusive of tumor resection. An iodine-based skin preparation solution was used just prior to draping patients, and an intravenous antibiotic with coverage of skin flora was administered within an hour prior to incision. An SSI case was defined as any in which additional management was required following resection because of wound breakdown, the presence of bacteria in wound drainage, or the need for reoperation for wound washout. Patients were then dichotomized into postoperative SSI and non-SSI cohorts.

Several metrics of performance or frailty were considered including the American Society of Anesthesiologists (ASA) status, Karnofsky Performance Status (KPS), and 5-factor modified frailty index (mFI-5). The mFI-5 accounts for diabetes mellitus, hypertension requiring medication, chronic obstructive pulmonary disease, congestive heart failure, and a nonindependent functional status defined as requiring assistance with activities of daily living.<sup>12</sup> Along with a continuous measure for KPS, we also dichotomized this index into scores  $\geq 70$  and  $< 70$  given that, beyond this threshold, patients are able to care for themselves. Additionally, this cutoff has been used in several previous studies as a predictor of important postoperative clinical outcomes.<sup>13–15</sup> Furthermore, we specifically recorded whether patients had a diagnosis of diabetes mellitus prior to surgery.

When available, preoperative nutritional data such as albumin level, albumin/globulin ratio (AGR), prognostic nutritional index (PNI), and nutritional risk index (NRI) were included in subanalyses. Previously established cutpoints for preoperative albumin, AGR, and PNI were used

to define nutritional status in our patient cohort. In brief, cases with values less than or equal to these cutpoints were considered to have a low nutrition status, which has been shown to be associated with lower postoperative survival in GBM patients.<sup>16</sup> The optimal albumin cutpoint used was 3.9 g/dl, the AGR cutpoint was 1.90, and the PNI cutpoint was 43.48. The NRI was classified according to the established categories of no risk (NRI  $> 100$ ), low risk (NRI 97.5–100), and moderate/severe risk (NRI  $\leq 97.5$ ).<sup>16</sup>

We considered the influence of patient exposure to steroids and antibiotic medications, aside from standard perioperative precautions, on the risk of postoperative SSI. In accordance with previous work, we grouped patients based on whether they received no steroids, only preoperative steroids, only postoperative steroids, or combined preoperative and postoperative steroids, all within 2 weeks of surgery (converted and standardized to milligrams of dexamethasone).<sup>17</sup> For consistency, preoperative antibiotic use was defined as any antibiotic medications taken within 2 weeks prior to surgery, and postoperative antibiotic use was defined as any antibiotic medications taken 2 weeks after discharge. Finally, total length of stay was obtained for each patient.

### Incision Type

Incision type was collected from operative notes and was categorized as linear/curvilinear, reverse question mark, trapdoor, or frontotemporal. Linear/curvilinear incisions included incisions marked in the operative notes as “linear” or “curvilinear.” Reverse question mark incisions spanned from the zygoma, curved posteriorly above the ear, and turned anteriorly to reach the region of the widow’s peak. Trapdoor incisions included surgeon references to “trapdoor” and “U-shaped” incisions within the operative notes. Frontotemporal incisions included “pterional,” “bicoronal,” and “bifrontal” incisions. Depictions of these incision types are presented in Fig. 1.

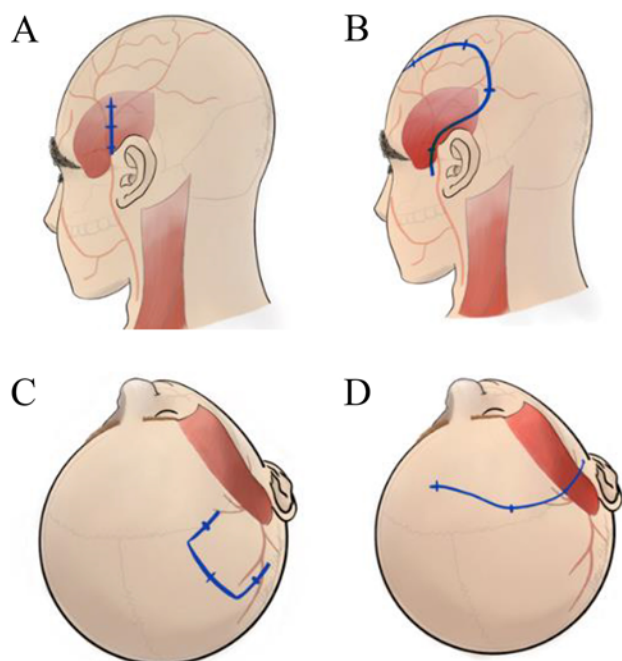
### Statistical Analyses

Data were recorded in Microsoft Excel 2016 (Microsoft Corp.), and all analyses were performed using R statistical software (R Foundation for Statistical Computing). For bivariate analysis, categorical variables were assessed via chi-square analyses, and continuous variables were assessed via Student t-tests. Significant clinical characteristics and predictors on either bivariate or univariable analysis were included in the multivariable analysis. In addition, incision type was included in the multivariable analysis. Given their high frequency and wide utility in our cohort, linear/curvilinear incisions were used as the reference for incision type in all analyses.

## Results

### Demographic and Clinical Characteristics of Entire Patient Cohort

Initially, our cohort consisted of 911 cases of craniotomy for GBM resection, with 30 instances (3.3%) of postoperative SSI. Of the 881 non-SSI cases, 260 were eliminated because of missing or unavailable clinical and



**FIG. 1.** Scalp incision classifications for patients undergoing craniotomy for GBM resection: linear/curvilinear (A), reverse question mark (B), trapdoor (C), and frontotemporal (D). Illustrations by Mazin Elshareif. Figure is available in color online only.

demographic data and 18 cases with miter incisions were removed, reducing our total cohort size to 633 cases. The mean patient age in these cases was  $58.3 \pm 13.6$  years, and 59.9% of the patients were male (Table 1). Most patients were White/Caucasian (83.6%) and non-Hispanic (96.1%). Preoperative KPS ranged from 20 to 100 in our cohort, with a mean of  $74.5 \pm 16.3$  and 24.8% of patients presenting with a preoperative KPS < 70. Of note, only 2 patients (0.32%) presented with a preoperative KPS of 20, both of whom were critically ill and were operated on as a lifesaving measure. Additionally, we observed a mean ASA status of  $2.68 \pm 0.63$  and mean mFI-5 of  $0.60 \pm 0.80$ . Prior to surgery, 14.2% of cases had a diagnosis of diabetes mellitus. For 80.4% of cases, the operation was a first-time GBM resection. The mean lead surgeon experience among all cases was  $20.6 \pm 8.97$  years. Data on preoperative nutritional indices were limited, with albumin data available for 324 cases, AGR data for 316 cases, PNI data for 304 cases, and NRI data for 190 cases. Based on these available data, low preoperative albumin was observed in 99 cases (30.6%), low AGR in 188 cases (59.5%), and low PNI in 73 cases (24.0%). Of the 190 patients with available NRI data, 25.3% were at risk for malnutrition. One hundred seventy-two patients (27.2%) had a history of radiation therapy prior to the date of surgery. The majority of patients (55.9%) were exposed to steroid regimens both before and after surgery. Additionally, most patients (55.6%) had linear/curvilinear incisions during craniotomy, with the trapdoor incision as the second most common (25.1%). A carmustine wafer was administered intraoperatively in a total of 54 patients (8.5%). The mean length of

**TABLE 1.** Demographic and clinical characteristics of 633 patients who underwent craniotomy for GBM resection

Characteristic	Value
<b>Demographic</b>	
Age in yrs	$58.3 \pm 13.6$
Male sex	379 (59.9)
<b>Race</b>	
White/Caucasian	529 (83.6)
Black/African American	38 (6.0)
Asian	14 (2.2)
Other	52 (8.2)
<b>Ethnicity</b>	
Hispanic	25 (3.9)
Non-Hispanic	608 (96.1)
<b>Preop clinical features</b>	
KPS	$74.5 \pm 16.3$
KPS <70	157 (24.8)
mFI-5 score	$0.60 \pm 0.80$
Diabetes	90 (14.2)
ASA status	$2.68 \pm 0.63$
<b>Resection no.</b>	
1st	509 (80.4)
2nd	101 (16.0)
3rd or more	23 (3.6)
Surgeon experience in yrs	$20.6 \pm 8.97$
<b>Preop nutritional status</b>	
Low albumin (n = 324)	99 (30.6)
Low AGR (n = 316)	188 (59.5)
Low PNI (n = 304)	73 (24.0)
<b>NRI (n = 190)</b>	
No risk	142 (74.7)
Low risk	16 (8.4)
Moderate/severe risk	32 (16.8)
Prior radiation history	172 (27.2)
<b>Steroid administration</b>	
None	65 (10.3)
Preop only	19 (3.0)
Postop only	195 (30.8)
Preop & postop	354 (55.9)
<b>Antibiotic exposure</b>	
Preop	262 (41.4)
Postop	331 (52.3)
<b>Incision type</b>	
Linear/curvilinear	352 (55.6)
Reverse question mark	78 (12.3)
Trapdoor	159 (25.1)
Frontotemporal	44 (7.0)
Carmustine wafer use	54 (8.5)
Length of stay in days	$5.77 \pm 6.90$

Values are expressed as mean  $\pm$  standard deviation or number (%).

**TABLE 2. Bivariate differences between patients with SSIs and those without following GBM resection**

	SSI Population	Non-SSI Population	p Value
No. of cases	30	603	
Demographic			
Age in yrs	56.3 ± 12.2	58.4 ± 13.7	0.41
Male sex	14 (46.7)	365 (60.5)	0.13
Race			
White/Caucasian	25 (83.3)	504 (83.6)	0.97
Non-White	5 (16.7)	99 (16.4)	0.97
Ethnicity			
Hispanic	0 (0.0)	25 (4.1)	0.25
Non-Hispanic	30 (100.0)	578 (95.9)	0.25
Preop clinical features			
KPS	63.0 ± 18.2	75.1 ± 16.0	<b>&lt;0.0001</b>
KPS <70	18 (60.0)	139 (23.1)	<b>0.0001</b>
mFI-5 score	0.67 ± 0.96	0.60 ± 0.80	0.64
Diabetes	6 (20.0)	84 (13.9)	0.36
ASA status	2.70 ± 0.70	2.67 ± 0.62	0.80
Resection no.			
1st	21 (70.0)	488 (80.9)	0.14
2nd	7 (23.3)	94 (15.6)	0.26
3rd or more	2 (6.7)	21 (3.5)	0.36
Surgeon experience in yrs	20.7 ± 7.77	20.6 ± 9.03	0.99
Preop nutritional status			
Low albumin (n = 324)	8 (38.1)	91 (30.0)	0.44
Low AGR (n = 188)	13 (61.9)	175 (60.0)	0.56
Low PNI (n = 73)	7 (36.8)	66 (23.2)	0.18
NRI (n = 190)			
No risk	6 (60.0)	136 (75.6)	0.27
Low risk	1 (10.0)	15 (8.33)	0.85
Moderate/severe risk	3 (30.0)	29 (16.1)	0.25
Prior radiation history	13 (43.3)	159 (26.4)	<b>0.042</b>
Steroid administration			
None	0 (0.0)	65 (10.8)	0.06
Preop only	0 (0.0)	19 (3.2)	0.32
Postop only	5 (16.7)	190 (31.5)	0.09
Preop & postop	25 (83.3)	329 (54.6)	<b>0.002</b>
Antibiotic exposure			
Preop	12 (40.0)	250 (41.5)	0.87
Postop	14 (46.7)	317 (52.6)	0.53
Incision type			
Linear/curvilinear	9 (30.0)	343 (56.9)	<b>0.004</b>
Reverse question mark	4 (13.3)	74 (12.3)	0.86
Trapdoor	13 (43.3)	146 (24.2)	<b>0.012</b>
Frontotemporal	4 (13.3)	40 (6.6)	0.16
Carmustine wafer use	5 (16.7)	49 (8.1)	0.10
Length of stay in days	7.20 ± 11.1	5.70 ± 6.62	0.25

Values are expressed as mean ± standard deviation or number (%), unless indicated otherwise. Boldface type indicates statistical significance.

stay for patients was  $5.77 \pm 6.90$  days. There were no cases of postoperative methicillin-resistant *Staphylococcus aureus* SSI in our cohort.

### Bivariate Differences in Clinical Presentations of SSI Versus Non-SSI Groups

Of the 633 cases included in our study, 30 had a postoperative SSI. Patients who experienced an SSI demonstrated a significantly lower preoperative KPS than the non-SSI patients (63.0 vs 75.1,  $p < 0.0001$ ) and a higher frequency of KPSs below 70 (60% vs 23.1%,  $p = 0.0001$ ; Table 2). Patients in the SSI group were also more likely to have undergone radiation therapy at any point prior to surgery (43.3% vs 26.4%,  $p = 0.042$ ) and to have received both preoperative and postoperative steroid treatments (83.3% vs 54.6%,  $p = 0.002$ ). Within the subset of patients receiving both preoperative and postoperative steroids, patients in the SSI cohort ( $344.9 \pm 228.1$  mg dexamethasone) had received a higher mean total dose than the non-SSI cohort ( $202.1 \pm 166.6$  mg dexamethasone;  $p < 0.001$ ). Between the SSI and non-SSI cohorts, there were no significant differences in age, sex, racial and ethnic composition, ASA status, mFI-5 score, prevalence of diabetes, number of surgeries, lead surgeon experience, preoperative nutritional metrics, carmustine wafer use, and length of stay.

### Bivariate Differences in Craniotomy Incision Type Between SSI and Non-SSI Groups

A comparison of craniotomy scalp incision types used during resection between the SSI and non-SSI groups is highlighted in Table 2. Patients in the non-SSI group were more likely to have had linear/curvilinear scalp incisions than the SSI group (56.9% vs 30.0%,  $p = 0.004$ ). Additionally, patients in the SSI group were more likely to have had trapdoor incisions than the non-SSI group (43.3% vs 24.2%,  $p = 0.012$ ). Both reverse question mark ( $p = 0.86$ ) and frontotemporal ( $p = 0.16$ ) incision types did not demonstrate any significant differences in frequency between the SSI and non-SSI groups.

### Predictors of Increased Postoperative SSI Risk

Each outlined clinical and demographic characteristic, along with each incision type, was individually evaluated via logistic regression. On this analysis, trapdoor incisions were found to be a significant predictor of postoperative SSI incidence (OR 3.44,  $p = 0.005$ ). Additionally, decreased KPS was also found to be a predictor of postoperative SSI incidence (OR 1.04,  $p = 0.0001$ ). Patient exposure to steroid administration both prior to and following surgery predicted an increased SSI risk on univariable analysis (OR 4.19,  $p = 0.00392$ ). The presence of diabetes and length of stay did not demonstrate a relationship on univariable analysis. And although significant on bivariate chi-square analysis, prior history of radiation therapy did not demonstrate significance on univariable analysis.

Multivariable analysis revealed trapdoor incisions, decreased KPS, and combined preoperative and postoperative steroid administration to be significant predictors of postoperative SSI (Table 3). Utilizing a trapdoor scalp incision during resection was independently associated with



an increased risk of postoperative SSI (OR 3.34, 95% CI 1.37–8.49,  $p = 0.008$ ). Single point decreases in the preoperative KPS were associated with an increased risk of developing postoperative SSI (OR 1.04, 95% CI 1.02–1.06,  $p = 0.0003$ ). Patients on steroids both before and after surgery independently predicted an increased risk of developing a postoperative SSI (OR 3.52, 95% CI 1.41–10.7,  $p = 0.013$ ). This model held significance for all three predictors when applied to the subset of 509 primary GBM resection patients. Combined preoperative and postoperative steroids, as well as trapdoor incisions, maintained a  $p$  value  $< 0.10$  for recurrent patients, whereas preoperative KPS demonstrated  $p = 0.13$ .

## Discussion

In the present study, we investigated a multitude of demographic and clinical presentations and their potential influence on the increased risk of postoperative SSI incidence. Additionally, we studied the relationship between the scalp incision type used during craniotomy and postoperative SSI risk. On multivariable analysis, a lower preoperative KPS, a trapdoor scalp incision, and combined preoperative and postoperative steroid administration were independently associated with an increased risk of SSI. This model held strongly when applied to patients undergoing resection of a primary GBM and tended to be associated with postoperative SSI when applied only to patients undergoing resection of a recurrent GBM.

## Prior Research

Postoperative SSIs have been shown to be strongly associated with hospital readmission and reoperation, which not only place a significant financial burden on hospitals, but also can hinder overall patient recovery.<sup>6,18</sup> In the literature, rates of SSI following cranial surgery range from 3.25% to 10% of patients.<sup>6,19</sup> While not directly examining SSI risk in patients with GBM, several studies have analyzed risk factors for SSI within neurosurgery. A 2017 systematic review from Fang et al. analyzed 26 studies of risk factors for SSI following craniotomy, finding that the presence of another infection, a greater number of previous operations, a lower ASA status, and male sex were all significant predictors of developing an SSI.<sup>20</sup> Similarly, prior studies by Patel et al. and Bekelis et al. found that an increased operative time was a significant predictor of SSI following cranial surgery.<sup>8,21</sup> Building on these results, Han and colleagues performed a meta-analysis of 5 studies on the effect of operative duration on the rate of SSI, finding that a longer operative time was associated with a higher rate of SSI.<sup>22</sup> While risk factors for other neurosurgical procedures have been well described, the characterization of SSI risk factors in resections for GBM has been limited.<sup>19</sup> A randomized clinical trial by Brem et al. and follow-up investigations by Attenello et al. and Chaichana et al. demonstrated that carmustine wafer use is not associated with postoperative infection in GBM patients undergoing resection.<sup>7,23,24</sup> Additionally, much prior research has evaluated intraoperative risk factors, and in our study we sought to evaluate the significance of preoperative considerations and craniotomy scalp incision type on SSI.

**TABLE 3. Multivariate logistic regression evaluating predictors of postoperative SSI among all study patients**

Variable	OR (95% CI)	p Value
Incision		
Linear/curvilinear	Reference	Reference
Reverse question mark	2.36 (0.61–7.70)	0.17
Trapdoor	3.34 (1.37–8.49)	<b>0.008</b>
Frontotemporal	3.19 (0.80–10.9)	0.07
Decreasing preop KPS	1.04 (1.02–1.06)	<b>0.0003</b>
Prior radiotherapy	2.00 (0.90–4.40)	0.08
Combined preop & postop steroid treatment	3.52 (1.41–10.7)	<b>0.013</b>

Boldface type indicates statistical significance.

## Influence of Functional Independence on SSI Incidence

Patients with brain tumors, especially malignant pathologies, often present with high morbidity, making them more susceptible to poor outcomes following invasive procedures.<sup>7</sup> Greater preoperative patient frailty has been well documented as a significant predictor of a host of poor outcomes in neurosurgery, including death, extended length of stay, higher cost of care, and nonroutine discharge disposition.<sup>25–27</sup> The predictive ability of preoperative KPS has been well documented and shown to be independently associated with hospital readmission and overall survival.<sup>28</sup> The KPS can be conveniently assessed and quickly communicates a patient's functional status prior to undergoing invasive surgery. However, the role of KPS in predicting the risk of postoperative SSI is less clear.<sup>29,30</sup> We found that a 10-point decrease in preoperative KPS was independently associated with a 4% elevated risk for postoperative SSI. We posit that patients with increased physical frailty or lower performance have a compromised recuperative ability, secondarily increasing their susceptibility to postoperative SSI. Lower degrees of functional independence can then result in patients applying more pressure on their wound from immobility or being unable to fully care for their incision, potentially compromising healing potential.<sup>31,32</sup> The KPS scale is convenient as a preoperative index, and a low KPS may effectively inform healthcare teams about which patients are at high risk for postoperative SSI.

## Impact of Trapdoor Scalp Incisions on Elevated SSI Risk

One critical goal of our study was to determine if the shape and characteristic of the incision itself demonstrated a relationship with postoperative SSI risk. We found that trapdoor scalp incisions were independently associated with an elevated likelihood of postoperative SSI, utilizing linear incisions as a reference. The relationship between incision types and healing mechanisms specifically in patients undergoing craniotomy for GBM resection has not been well investigated. Some studies in the plastic surgery literature have proposed that trapdoor incisions/scars are susceptible to poor healing because of the concentric contraction of curved scars.<sup>33,34</sup> Additionally, we propose that a contributing factor may be that trapdoor incisions may

transect feeding arterioles, which could secondarily compromise healing potential.

### Relationship Between Steroid Utilization and SSI Risk

Prior literature has suggested that steroid use in patients undergoing craniotomy for tumor resection may contribute to an increased risk of postoperative SSI. A 2021 study by Medikonda et al. highlighted that combined preoperative and postoperative dexamethasone demonstrated a trend toward an increased incidence of postoperative SSI in a cohort of 451 glioma patients ( $p = 0.08$ ).<sup>17</sup> Our results expand on these past findings by more robustly investigating this relationship specifically in patients with GBM. Interestingly, within this combined treatment group we observed a higher average total steroid dose for patients who developed an SSI than that in patients who did not ( $p < 0.001$ ).

Steroids such as dexamethasone have historically been used in neurosurgery to manage cerebral edema, which may commonly occur in the presence of brain tumors.<sup>35</sup> However, these drugs are associated with several adverse side effects including hyperglycemia and immunosuppression.<sup>36,37</sup> Thus, administration of these medications requires a nuanced approach to determine which patients should be given steroids and the proper surveillance for those undergoing such management. It is possible that in patients with aggressive tumors such as GBM, reducing immune function via steroid administration may compromise a patient's recovery, making them more susceptible to wound infections. Prior studies have demonstrated that in patients with poor glycemic control, this risk is even more accentuated, further suggesting that prolonged steroid utilization may have an important role in predicting the individualized risk of postoperative SSI in patients undergoing GBM resection.<sup>38</sup> Given the findings of the current study, our surgeons are actively engaging in a division-wide, prospective, quality improvement effort to minimize steroid use in the perioperative period, and we hope to report on these results in a future study.

### Current and Future Strategies for SSI Prevention

Because of the high morbidity associated with infections, there have been several published efforts to reduce the incidence of SSIs. Many of these interventions have centered around preventative care bundles. Such care bundles involve many perioperative considerations including preoperative bathing, weight-based antibiotic prophylaxis, wound care education, and postoperative glycemic control. Nevertheless, there is no consensus on the efficacy of such measures, with conflicting results on their success in the literature. In a 2015 study, Schaffzin et al. examined postoperative SSI prevention following cardiothoracic and neurosurgical procedures and reported that the adoption of a multistage care bundle reduced hospital network SSIs by 21%.<sup>39</sup> This work was further corroborated in a 2019 study by Arocho-Quinones and colleagues, who found that infection prevention bundles significantly reduced SSI rates following several types of neuromodulation surgery.<sup>40</sup>

However, these results were contradicted by many similar efforts in which care bundles did not demonstrate significant SSI reduction. For instance, a study by Davies

et al. revealed that evidence-based care bundles centered around antibiotic prophylaxis and glycemic control following cranial surgery did not significantly reduce SSI.<sup>41</sup> Additionally, a 2017 prospective study by Uzuka et al. demonstrated that the implementation of a care bundle in three neurosurgical units did not significantly reduce SSI incidence following malignant brain tumor resection.<sup>6</sup> This equipoise points to an important need for future studies analyzing larger, multiinstitutional patient cohorts to identify core predictors of increased SSI risk in cranial neurosurgery, as well as interventions to help reduce their incidence.

These findings point to several strategies to better prevent SSI. First, our finding of trapdoor incisions elevating the risk of postoperative SSI may spark future collaborative decision-making regarding craniotomy incision planning between neurosurgeons and plastic surgeons, especially for challenging cases. Such a multidisciplinary approach may help to modify existing routine incisions used during these procedures, with an emphasis on maximizing healing potential following surgery, as has already been demonstrated in the growing neuroplastic surgery literature.<sup>42–44</sup> Second, care bundles aimed at preventing SSI should incorporate reduced steroid use, unless absolutely necessary. Our study demonstrated that patients who had received both preoperative and postoperative steroids were most susceptible to postoperative SSIs, likely in part because of their continued immunosuppression compromising optimal healing capacity. This is a modifiable factor that should be considered moving forward in investigating SSI reduction specifically in GBM patients.

### Study Limitations

Our study is retrospective in nature; thus, we were unable to determine causality for our considered predictors. Because of limitations in data availability, we were unable to investigate the effect of prealbumin, as it relates to malnutrition, or other molecular markers, including CKD1 mutation and TERT promoter mutation, on postoperative SSI. Furthermore, studies on specific thresholds of steroid dosage predicting SSIs are warranted. Additionally, our patient cohort is only representative of patients treated at our institution within a definitive time period. Therefore, external validation in larger, multiinstitutional cohorts is warranted to further study and build on our results. Additionally, our study only involves patients presenting with GBM. Although these results may help to guide future research and supplement the existing body of literature, they may not be generalizable to other pathologies.

### Conclusions

Our study is among the first to analyze specific predictive factors for postoperative SSI specifically in patients undergoing craniotomy for GBM resection. Our findings that a lower preoperative KPS, a trapdoor scalp incision, and combined preoperative and postoperative steroid treatments were predictive of SSI incidence may help surgeons in identifying which patients have an elevated risk of postoperative SSI while guiding incision and treatment choices in these cases.

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## References

1. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352(10):987-996.
2. Komotar RJ, Otten ML, Moise G, Connolly ES Jr. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma—a critical review. *Clin Med Oncol*. 2008;2:421-422.
3. Lebo NL, Quimby AE, Caulley L, et al. Surgical site infection affects length of stay after complex head and neck procedures. *Laryngoscope*. 2020;130(12):E837-E842.
4. Chiang HY, Kamath AS, Pottinger JM, et al. Risk factors and outcomes associated with surgical site infections after craniotomy or craniectomy. *J Neurosurg*. 2014;120(2):509-521.
5. Young PY, Khadaroo RG. Surgical site infections. *Surg Clin North Am*. 2014;94(6):1245-1264.
6. Uzuka T, Takahashi H, Nakasu Y, et al. Surgical site infection after malignant brain tumor resection: a multicenter study for induction of a basic care bundle. *Neurol Med Chir (Tokyo)*. 2017;57(10):542-547.
7. Chaichana KL, Kone L, Bettgowda C, et al. Risk of surgical site infection in 401 consecutive patients with glioblastoma with and without carmustine wafer implantation. *Neurol Res*. 2015;37(8):717-726.
8. Bekelis K, Coy S, Simmons N. Operative duration and risk of surgical site infection in neurosurgery. *World Neurosurg*. 2016;94:551-555.e6.
9. Buchanan IA, Donoho DA, Patel A, et al. Predictors of surgical site infection after nonemergent craniotomy: a Nationwide Readmission Database analysis. *World Neurosurg*. 2018;120:e440-e452.
10. Lau D, Deviren V, Ames CP. The impact of surgeon experience on perioperative complications and operative measures following thoracolumbar 3-column osteotomy for adult spinal deformity: overcoming the learning curve. *J Neurosurg Spine*. 2019;32(2):207-220.
11. Cahill PJ, Pahys JM, Asghar J, et al. The effect of surgeon experience on outcomes of surgery for adolescent idiopathic scoliosis. *J Bone Joint Surg Am*. 2014;96(16):1333-1339.
12. Subramaniam S, Aalberg JJ, Soriano RP, Divino CM. New 5-Factor Modified Frailty Index using American College of Surgeons NSQIP data. *J Am Coll Surg*. 2018;226(2):173-181.e8.
13. Sofietti R, Ducati A, Rudà R. Brain metastases. *Handb Clin Neurol*. 2012;105:747-755.
14. Sacko A, Hou MM, Temgoua M, et al. Evolution of the Karnofsky Performance Status throughout life in glioblastoma patients. *J Neurooncol*. 2015;122(3):567-573.
15. Harlay V, Loundou A, Boucard C, et al. P11.04 Autonomy duration as analyzed by KPS $\geq$ 70 cumulative time in patients with biopsy-only glioblastoma (BO-GBM). A sub-analysis of the Timone cohort. *Neuro Oncol*. 2021;23(suppl 2):ii29-ii29.
16. Huq S, Khalafallah AM, Botros D, et al. The prognostic impact of nutritional status on postoperative outcomes in glioblastoma. *World Neurosurg*. 2021;146:e865-e875.
17. Medikonda R, Patel K, Jackson C, et al. The safety and efficacy of dexamethasone in the perioperative management of glioma patients. *J Neurosurg*. 2021;136(4):1062-1069.
18. Ke C, Jin Y, Evans H, et al. Prognostics of surgical site infections using dynamic health data. *J Biomed Inform*. 2017;65:22-33.
19. Salle H, Deluche E, Couvé-Deacon E, et al. Surgical site infections after glioblastoma surgery: results of a multicentric retrospective study. *Infection*. 2021;49(2):267-275.
20. Fang C, Zhu T, Zhang P, Xia L, Sun C. Risk factors of neurosurgical site infection after craniotomy: a systematic review and meta-analysis. *Am J Infect Control*. 2017;45(11):e123-e134.
21. Patel S, Thompson D, Innocent S, Narbad V, Selway R, Barakas K. Risk factors for surgical site infections in neurosurgery. *Ann R Coll Surg Engl*. 2019;101(3):220-225.
22. Han C, Song Q, Ren Y, Luo J, Jiang X, Hu D. Dose-response association of operative time and surgical site infection in neurosurgery patients: a systematic review and meta-analysis. *Am J Infect Control*. 2019;47(11):1393-1396.
23. Brem H, Piantadosi S, Burger PC, et al. Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. *Lancet*. 1995;345(8956):1008-1012.
24. Attenello FJ, Mukherjee D, Datto G, et al. Use of Gliadel (BCNU) wafer in the surgical treatment of malignant glioma: a 10-year institutional experience. *Ann Surg Oncol*. 2008;15(10):2887-2893.
25. Jimenez AE, Khalafallah AM, Lam S, et al. Predicting high-value care outcomes after surgery for skull base meningiomas. *World Neurosurg*. 2021;149:e427-e436.
26. Jimenez AE, Shah PP, Khalafallah AM, et al. Patient-specific factors drive intensive care unit and total hospital length of stay in operative patients with brain tumor. *World Neurosurg*. 2021;153:e338-e348.
27. Khalafallah AM, Huq S, Jimenez AE, Brem H, Mukherjee D. The 5-factor modified frailty index: an effective predictor of mortality in brain tumor patients. *J Neurosurg*. 2021;135(1):78-86.
28. Lacroix M, Abi-Said D, Fourney DR, et al. A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. *J Neurosurg*. 2001;95(2):190-198.
29. Thuluvath PJ, Thuluvath AJ, Savva Y. Karnofsky performance status before and after liver transplantation predicts graft and patient survival. *J Hepatol*. 2018;69(4):818-825.
30. Huq S, Khalafallah AM, Patel P, et al. Predictive model and online calculator for discharge disposition in brain tumor patients. *World Neurosurg*. 2021;146:e786-e798.
31. Fyllingen EH, Oldervoll LM, Loge JH, et al. Computer-based assessment of symptoms and mobility in palliative care: feasibility and challenges. *J Pain Symptom Manage*. 2009;38(6):827-836.
32. Hendrichova I, Castelli M, Mastroianni C, et al. Pressure ulcers in cancer palliative care patients. *Palliat Med*. 2010;24(7):669-673.
33. Kim CH, Son KM, Choi WY, Cheon JS. Evaluation of triamcinolone injection and subcision as a first-line non-surgical treatment of post-traumatic acute trap-door deformity. *Arch Aesthetic Plast Surg*. 2018;24(2):62-67.
34. Koranda FC, Webster RC. Trapdoor effect in nasolabial flaps. Causes and corrections. *Arch Otolaryngol*. 1985;111(7):421-424.
35. Kostaras X, Cusano F, Kline GA, Roa W, Easaw J. Use of dexamethasone in patients with high-grade glioma: a clinical practice guideline. *Curr Oncol*. 2014;21(3):e493-e503.
36. Burkhardt T, Czorlich P, Mende KC, et al. Postoperative nausea and vomiting following craniotomy: risk factors and complications in context of perioperative high-dose dexamethasone application. *J Neurol Surg A Cent Eur Neurosurg*. 2019;80(5):381-386.
37. Hempen C, Weiss E, Hess CF. Dexamethasone treatment in patients with brain metastases and primary brain tumors: do the benefits outweigh the side-effects? *Support Care Cancer*. 2002;10(4):322-328.
38. Corcoran TB, Myles PS, Forbes AB, et al. Dexamethasone and surgical-site infection. *N Engl J Med*. 2021;384(18):1731-1741.
39. Schaffzin JK, Harte L, Marquette S, et al. Surgical site infection reduction by the solutions for patient safety hospital engagement network. *Pediatrics*. 2015;136(5):e1353-e1360.

40. Arocho-Quinones EV, Huang CC, Ward BD, Pahapill PA. Care bundle approach to minimizing infection rates after neurosurgical implants for neuromodulation: a single-surgeon experience. *World Neurosurg*. 2019;128:e87-e97.
41. Davies BM, Jones A, Patel HC. Implementation of a care bundle and evaluation of risk factors for surgical site infection in cranial neurosurgery. *Clin Neurol Neurosurg*. 2016;144:121-125.
42. Ibrahim Z, Santiago GF, Huang J, Manson PN, Gordon CR. Algorithmic approach to overcome scalp deficiency in the setting of secondary cranial reconstruction. *J Craniofac Surg*. 2016;27(1):229-233.
43. Wolff A, Santiago G, Weingart J, Huang J, Gordon CR. Introducing the rectus fascia scalp augmentation technique: a new method for improving scalp durability in cranioplasty reconstruction. *J Craniofac Surg*. 2018;29(7):1733-1736.
44. Wolff AY, Santiago GF, Belzberg M, et al. Full-thickness skin grafting for local defect coverage following scalp adjacent tissue transfer in the setting of cranioplasty. *J Craniofac Surg*. 2019;30(1):115-119.

## Disclosures

Dr. Bettegowda is a consultant for DePuy Synthes, Bionaut Labs, and Galectin Therapeutics. Dr. Brem is a consultant for InSightec, Accelerating Combination Therapies, Catelio Nexus Fund II

LLC, LikeMinds Inc., Galen Robotics Inc., Candel Therapeutics, and Nurami Medical; serves on the Scientific Advisory Board of Candel Therapeutics; and has stock in and serves on the Board of Directors of CraniUS.

## Author Contributions

Conception and design: Mukherjee, Nair. Acquisition of data: Mukherjee, Nair, Botros, Chakravarti, Mao, Wu, Lu, Liu, Elshareif. Analysis and interpretation of data: Mukherjee, Nair, Botros, Chakravarti, Mao, Wu, Lu, Liu, Elshareif. Drafting the article: Nair, Botros, Mao, Wu, Lu, Liu, Elshareif. Critically revising the article: Mukherjee, Nair, Botros, Chakravarti, Jackson, Gallia, Bettegowda, Weingart, Brem. Reviewed submitted version of manuscript: Mukherjee, Nair, Botros, Chakravarti, Jackson, Gallia, Bettegowda, Weingart, Brem. Approved the final version of the manuscript on behalf of all authors: Mukherjee. Statistical analysis: Nair, Botros. Study supervision: Mukherjee.

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