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The effect of preoperative steroids for at least 10 days on complications following craniotomy for tumor resection: A database, retrospective cohort study

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ABSTRACT

Introduction: The effect of chronic steroid therapy on postoperative outcomes after craniotomy for tumor resection remains understudied.
Research question: This study aimed to fill this gap and to identify risk factors of postoperative morbidity and mortality among patients on chronic steroid use undergoing craniotomy for tumor resection.
Materials and methods: Data from the American College of Surgeons National Surgical Quality Improvement Program were used. Patients who underwent craniotomy for tumor resection between 2011 and 2019 were included. Perioperative characteristics and complications were compared among patients with and without chronic steroid therapy, defined as steroid use for at least 10 days. Multivariable regression analyses were conducted to assess the impact of steroid therapy on postoperative outcomes. Subgroup analyses involving patients on steroid therapy were conducted to explore risk factors of postoperative morbidity and mortality.
Results: Of 27,037 patients, 16.2% were on steroid therapy. On regression analyses, steroid use was significantly associated with any postoperative complication, infectious complication, urinary tract infection, septic shock, wound dehiscence, pneumonia, non-infectious, pulmonary, and thromboembolic complications, cardiac arrest, blood transfusion, unplanned reoperation, readmission, and mortality. On subgroup analysis, risk factors for postoperative morbidity and mortality among patients on steroid therapy included older age, higher American Society of Anesthesiology physical status, functional dependence, pulmonary and cardiovascular comorbidities, anemia, dirty/infected wounds, prolonged operative time, disseminated cancer, and a diagnosis of meningioma.
Discussion and conclusion: Preoperative brain tumor patients on steroids for 10 or more days are at a relatively high risk of postoperative complications. We recommend a judicious use of steroids in brain tumor patients, both in terms of dosage and duration of treatment.

1. Introduction

Craniotomy is one of the commonest procedures in neurosurgery (Kuroda et al., 2004). Common indications for craniotomy include resection of brain tumors, reduction of elevated intracranial pressures, excision of brain abscesses, and evacuation of intracerebral hematomas (Donovan et al., 2006). Being a highly invasive procedure, craniotomy is associated with significant postoperative complications, including intracranial hemorrhages, tension pneumocephalus, soft tissue infections, and surgical site infections (Chughtai et al., 2019).

In patients undergoing craniotomy for tumor resection, steroids are often used to alleviate peritumor edema and mass effect preoperatively, allowing improvements in associated symptoms, such as headache, seizures, and even neurological deficits (Deutsch et al., 2013). In addition, brain tumor patients may also have concomitant comorbidities necessitating chronic steroid therapy (Carr et al., 2019). While steroid use for peritumor edema is known for its beneficial effects, chronic steroid therapy for concomitant comorbidities might predispose patients to immunosuppression, metabolic syndrome, osteoporosis, and delayed wound healing (Grennan and Wang, 2019; Ismael et al., 2011).

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Evidence from studies on spine surgery suggests increased risk of postoperative complications with chronic steroid therapy (White et al., 2019; Cloney et al., 2018). However, despite the frequency of steroid use and its potential impact on postoperative outcomes, chronic steroid therapy has been understudied among patients undergoing craniotomy for tumor resection, and existing results are contradictory. There is some evidence suggesting no adverse impact of chronic steroid use on postoperative complications in this cohort (Alan et al., 2015). In contrast, Lieber et al. identified steroid use as an independent risk factor of organ/space surgical site infections (SSIs) following craniotomy (Lieber et al., 2016). Merkler et al. further associated steroid use with infectious complications following neurosurgery, including organ/space SSI and pneumonia (Merkler et al., 2014).

In this study, we assessed the impact of preoperative chronic steroid therapy on postoperative morbidity and mortality in this cohort using a multi-institutional database. In addition, we also explored risk factors of postoperative morbidity and mortality specifically in patients requiring chronic steroid therapy.

2. Methods

2.1. Study design, data source & population

The American College of Surgeons National Surgical Quality Improvement Program was used in this multicenter, database, retrospective cohort analysis (ACS-NSQIP). The ACS-NSQIP is a prospectively maintained, risk-adjusted, multi-institutional registry with over 700 participating hospitals. The ACS-NSQIP's sampling technique, data collection measures, variables, and outcomes are detailed elsewhere (Khuri et al., 2007). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines were used to report this study. The Ethics Review Committee (ERC) at the Aga Khan University in Karachi, Pakistan, approved this study as an exemption from review (reference ID 2021-6715-19037).

This study included all adult patients (age $\geq$18 years) who had a supratentorial or infratentorial craniotomy for tumor resection. The current procedural terminology (CPT) codes were used to identify craniotomy cases (Table S1, Supplementary Appendix). Diagnoses of brain tumors were confirmed using the International Classification of Diseases, Ninth and Tenth Revisions, Clinical Modification (ICD-9-CM and ICD-10-CM) codes. Only cases from January 1, 2011, and December 31, 2019, were included to maintain consistency in the ACS-NSQIP definition of chronic steroid therapy. Exclusion criteria comprised of emergency cases and cases with operative time <90 min to exclude biopsy-only cases.

2.2. Measures

Sociodemographic characteristics were extracted for each patient, including age, gender, race, and body mass index (BMI). Patients were classified into the following categories based on BMI: healthy (18.5 to less than 25 kg/m^2), underweight (less than 18.5 kg/m^2), overweight (25.0 to less than 30 kg/m^2), and obese (30 kg/m^2 or more). Comorbidities included smoking, American Society of Anesthesiology (ASA) physical status, diabetes mellitus, functional health status, pulmonary, cardiovascular, and renal diseases, and anemia. Positive smoking status was classified as smoking within one year of craniotomy. Pulmonary comorbidity was a composite of chronic obstructive pulmonary disease (COPD) and ventilator dependence. Hypertension requiring medication and congestive heart failure were included in cardiovascular diseases. Renal comorbidity was a composite of preoperative dialysis or acute renal failure. Anemia was categorized as hematocrit <40% and <36% in males and females, respectively. Perioperative variables extracted were wound classification, operative time, surgery type, and postoperative diagnosis. Surgery types were categorized as supratentorial or infratentorial based on CPT codes. Postoperative diagnoses were classified as intrinsic brain tumor, meningioma, metastatic tumor, or other intracranial tumor based on the ICD-9-CM and ICD-10-CM codes (Table S2, Supplementary Appendix).

2.3. Steroid & non-steroid groups

Eligible patients were classified into the steroid and non-steroid groups. Patients receiving consistent administration of oral or parenteral steroids or other immunosuppressant medications for at least 10 days within the 30-day period prior to craniotomy were included in the steroid group. Remaining patients formed the non-steroid group, including those taking one-time steroid pulse, limited short course, or a taper of <10 days (Khuri et al., 2007). In addition, since patients with peritumor edema most often require steroids for a brief preoperative period, these patients likely became part of the non-steroid group (Bebawy, 2012; Dixit and Kumthekar, 2020).

2.4. Outcomes

Primary outcomes included any 30-day postoperative complication, infectious complication, non-infectious complication, and all-cause mortality. Any postoperative complication was a composite of infectious and non-infectious complications. Infectious complications comprised of SSIs (superficial, deep, or organ/space), pneumonia, urinary tract infections (UTIs), sepsis, septic shock, and wound dehiscence. Non-infectious complications included cardiac, pulmonary, renal, and thromboembolic complications, stroke/cerebrovascular accident (CVA), and intraoperative/postoperative blood transfusion. Cardiac complications included myocardial infarction or cardiac arrest. Prolonged ventilation (>48 h) and unplanned reintubation comprised pulmonary complications. Renal complication was a composite of postoperative acute renal failure and progressive renal insufficiency. Thromboembolic complications included deep vein thrombosis and pulmonary embolism. Other outcomes were prolonged length of stay, unplanned reoperation, and unplanned readmission. Prolonged length of stay was defined as hospital stay for $\geq$8 days during the index admission.

2.5. Statistical analysis

Patients were segregated across steroid status. Descriptive statistics were presented. Non-parametric distributions of continuous variables, including age, BMI, operation time, and length of stay, were confirmed using Kolmogorov–Smirnov tests ($p<0.001$ for all). Accordingly, medians and interquartile ranges were used to describe continuous variables, and Mann-Whitney U tests were computed to compare their differences among patients with and without steroid therapy. Categorical variables were described using frequencies and percentages, and their differences across patients with and without steroid therapy were assessed using $\chi 2$ tests or Fisher's exact tests as appropriate. Missing data were reported in tables, allowing for consistent denominators in calculations.

Multivariable binary logistic regression models were computed to explore the impact of chronic steroid therapy on postoperative complications. These models were adjusted for clinically important covariates with $p<0.20$ on univariate analysis, including age, gender, race, BMI, smoking status, ASA physical status, diabetes mellitus, functional health status, pulmonary comorbidities, cardiovascular disease, renal disease, anemia, wound classification, operation time, postoperative diagnosis, and surgery type.

Subgroup analyses including only patients with chronic steroid therapy were performed. Patients were categorized into no complication and at least one complication groups. Univariate analyses were conducted to compare baseline characteristics, comorbidities, and operative variables across the two groups using Mann-Whitney U tests for continuous variables and $\chi 2$ tests or Fisher's exact tests for categorical variables. Characteristics with $p<0.20$ were included in multivariable binary

logistic regression models to explore risk factors of any complication, infectious complications, non-infectious complications, and mortality among patients on chronic steroid therapy.

Two-sided statistical analyses were used, and the threshold for statistical significance was set at $p<0.05$. Adjusted odds ratios (OR) and their 95% confidence intervals (CIs) were reported. The IBM SPSS (Statistical Package for Social Sciences) Version 26 was used for analyses.

3. Results

3.1. Patient characteristics

We identified 27,037 eligible patients (Fig. 1). A majority of the patients were females and white (54.0% [14,612 of 27,035] and 87.3% [19,098 of 21,865], respectively). Majority of patients underwent supratentorial surgery (77.4% [20,935 of 27,037]), with other clinicodemographic characteristics reported in Table 1.

A total of 4,386 patients (16.2% [4,386 of 27,037]) were included in the steroid group. Compared to non-steroid group, patients receiving steroids were more likely to be aged 61 to 80 years, females, and white. Steroid use was also associated with BMI, smoking status, higher ASA physical statuses, diabetes mellitus, partially or totally dependent functional health status, pulmonary, cardiovascular, and renal diseases, and anemia. In addition, patients in the steroid group were more likely to have contaminated and dirty/infected wounds, higher operative time, metastatic tumors, and supratentorial surgeries (Table 1).

3.2. Complications

Univariate analyses demonstrated significantly higher incidence of postoperative complications in the steroid vs non-steroid group (17.1% vs 12.0%; $p<0.001$) (Table 2). Compared to patients without chronic steroid therapy, those in steroid group were significantly more likely to develop infectious complications, UTIs, sepsis, septic shock, wound dehiscence, pneumonia, non-infectious complications, cardiac arrest, pulmonary and thromboembolic complications, blood transfusions, unplanned reoperations, and readmissions. In addition, incidences of prolonged length of hospital stay and mortality were also significantly higher in steroid vs non-steroid group.

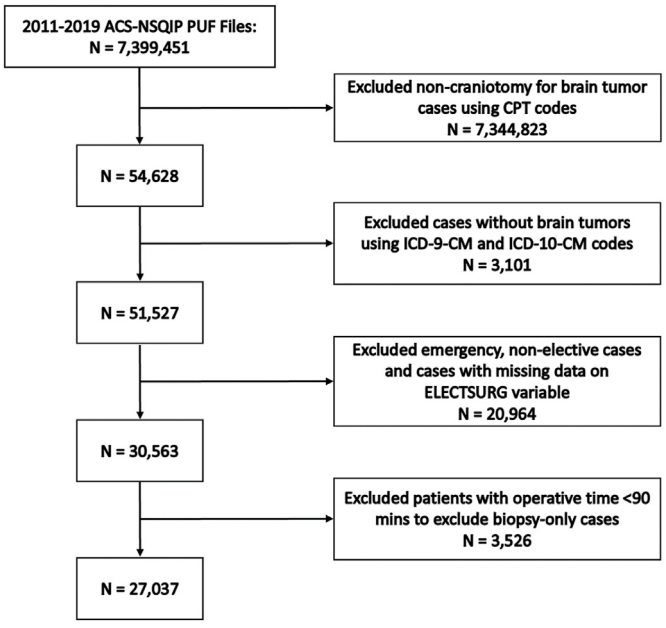

Fig. 1. Cohort creation
CPT: Current Procedural Terminology; ICD: International Classification of Diseases.

Table 1
Baseline characteristics, comorbidities, and operative variables stratified by chronic steroid therapy status.

Variable	No steroids N = 22651	Steroids N = 4386	P-value
Age/years[a]	56.0 (22.0)	59.0 (18.0)	<0.001
Age/years			
18 to 40	4523 (20.0%)	596 (13.6%)	<0.001
41 to 60	9391 (41.5%)	1798 (41.0%)	
61 to 80	8147 (36.0%)	1869 (42.6%)	
More than 80	584 (2.6%)	122 (2.8%)	
Missing	6	1	
Gender			
Female	12329 (54.4%)	2283 (52.1%)	0.004
Male	10321 (45.6%)	2102 (47.9%)	
Missing	1	1	
Race			
White	15891 (87%)	3207 (89.1%)	<0.001
Black	1013 (5.5%)	134 (3.7%)	
American Indian or Alaska Native	1293 (7.1%)	239 (6.6%)	
Asian, Native Hawaiian, or Pacific Islander	70 (0.4%)	18 (0.5%)	
Missing	4384	788	
BMI (kg/m^2)[a]	28.0 (8.1)	27.9 (7.6)	0.014
BMI (kg/m^2)			
Healthy (18.5 to <25)	6129 (27.5%)	1186 (27.4%)	0.037
Underweight (<18.5)	320 (1.4%)	79 (1.8%)	
Overweight (25.0 to <30)	7545 (33.8%)	1522 (35.2%)	
Obese (30 or higher)	8324 (37.3%)	1541 (35.6%)	
Missing	333	58	
Current smoker	3440 (15.2%)	774 (17.6%)	<0.001
ASA classification			
ASA 1-2	7627 (33.8%)	913 (21.0%)	<0.001
ASA 3-5	14906 (66.2%)	3444 (79.0%)	
Missing	118	29	
Diabetes mellitus	2542 (11.2%)	586 (13.4%)	<0.001
Functional health status			
Independent	21957 (97.3%)	4105 (94.1%)	<0.001
Partially dependent	535 (2.4%)	222 (5.1%)	
Totally dependent	80 (0.4%)	36 (0.8%)	
Missing	79	23	
Pulmonary comorbidities	605 (2.7%)	258 (5.9%)	<0.001
Cardiovascular disease	8154 (36.0%)	1702 (38.8%)	<0.001
Renal disease	36 (0.2%)	14 (0.3%)	0.024
Anemia			
No	17932 (83.0%)	3283 (77.3%)	<0.001
Yes	3664 (17.0%)	965 (22.7%)	BAS101725
Missing	1055	138	
Wound classification			
Clean	22200 (98%)	4275 (97.5%)	<0.001
Clean contaminated	286 (1.3%)	30 (0.7%)	
Contaminated	136 (0.6%)	65 (1.5%)	
Dirty/infected	29 (0.1%)	16 (0.4%)	
Operative time/minutes[a]	209.0 (152.0)	194.0 (128.0)	<0.001
Operative time/minutes			
90 to 180	8721 (38.5%)	1913 (43.6%)	<0.001
180 to <300	8250 (36.4%)	1650 (37.6%)	
More than 300	5680 (25.1%)	823 (18.8%)	
Postoperative diagnosis			
Intrinsic Brain Tumor	9729 (43%)	1942 (44.3%)	<0.001
Meningioma	7077 (31.2%)	875 (19.9%)	
Metastatic	2457 (10.8%)	1263 (28.8%)	
Other Neoplasms	3388 (15.0%)	306 (7.0%)	
Surgery type			
Supratentorial	17210 (76.0%)	3725 (84.9%)	<0.001
Infratentorial	5441 (24.0%)	661 (15.1%)	

[a] Reported with median and interquartile range; percentages are presented in columns; BMI: body mass index; ASA: American Society of Anesthesiology; pulmonary comorbidities included ventilator dependence and chronic obstructive pulmonary disease; cardiovascular disease included hypertension requiring medications and congestive heart failure; renal disease included acute renal failure and preoperative dialysis.

Table 2
30-day postoperative complications, stratified by chronic steroid therapy status.

Variable	No steroids N = 22651	Steroids N = 4386	P-value
Any complication	2723 (12.0%)	751 (17.1%)	<0.001
Infectious complications	1186 (5.2%)	352 (8.0%)	<0.001
Surgical site infection	504 (2.2%)	116 (2.6%)	0.089
Superficial	169 (0.7%)	36 (0.8%)	0.602
Deep incisional	96 (0.4%)	22 (0.5%)	0.474
Organ/space	252 (1.1%)	63 (1.4%)	0.067
Urinary tract infection	320 (1.4%)	102 (2.3%)	<0.001
Sepsis	260 (1.1%)	71 (1.6%)	0.009
Septic shock	65 (0.3%)	38 (0.9%)	<0.001
Wound disruption	55 (0.2%)	20 (0.5%)	0.014
Pneumonia	310 (1.4%)	104 (2.4%)	<0.001
Non-infectious complications	1930 (8.5%)	515 (11.7%)	<0.001
CVA/stroke with neurological deficit	352 (1.6%)	72 (1.6%)	0.669
Cardiac complications	102 (0.5%)	28 (0.6%)	0.099
Myocardial infarction	46 (0.2%)	8 (0.2%)	0.779
Cardiac arrest requiring CPR	60 (0.3%)	22 (0.5%)	0.009
Pulmonary complications	516 (2.3%)	136 (3.1%)	0.001
Ventilator >48 h	340 (1.5%)	87 (2.0%)	0.019
Unplanned reintubation	381 (1.7%)	99 (2.3%)	0.008
Renal complications	31 (0.1%)	7 (0.2%)	0.713
Progressive renal insufficiency	21 (0.1%)	3 (0.1%)	0.786
Acute renal failure	11 (0.0%)	4 (0.1%)	0.287
Thromboembolism	539 (2.4%)	189 (4.3%)	<0.001
Pulmonary embolism	244 (1.1%)	89 (2.0%)	<0.001
DVT/thrombophlebitis	384 (1.7%)	137 (3.1%)	<0.001
Blood transfusion	806 (3.6%)	192 (4.4%)	0.008
Unplanned reoperation	1034 (4.6%)	259 (5.9%)	<0.001
Unplanned readmission	2180 (9.7%)	635 (14.6)	<0.001
Prolonged length of stay	3115 (13.8%)	658 (15.1%)	0.028
Mortality	228 (1.0%)	115 (2.6%)	<0.001

Percentages are presented in columns; CVA: cerebrovascular accident; CPR: cardiopulmonary resuscitation; DVT: deep vein thrombosis.

On adjusted analysis, chronic steroid use was associated with any postoperative complication (OR 1.481, 95% CI 1.330–1.649), infectious complication (OR 1.522, 95% CI 1.308–1.770), UTI (OR 1.687, 95% CI 1.287–2.212), septic shock (OR 3.111, 95% CI 1.952–4.957), wound dehiscence (OR 2.158, 95% CI 1.060–4.393), pneumonia (OR 1.579, 95% CI 1.205–2.070), non-infectious complication (OR 1.421, 95% CI 1.256–1.609), cardiac arrest (OR 1.977, 95% CI 1.150–3.397), pulmonary complication (OR 1.351, 95% CI 1.081–1.687), thromboembolism (OR 1.767, 95% CI 1.453–2.149), blood transfusion (OR 1.320, 95% CI 1.084–1.607), unplanned reoperation (OR 1.414, 95% CI 1.200–1.666), unplanned readmission (OR 1.414, 95% CI 1.265–1.581), and mortality (OR 1.798, 95% CI 1.376–2.349) (Table 3).

3.3. Subgroup analyses

Subgroup analyses included only patients with chronic steroid use (16.2%; 4,386 of 27,037). On univariate comparison, patients with and without any postoperative complication significantly differed in terms of age ($p<0.001$), gender ($p = 0.010$), race ($p = 0.032$), BMI ($p = 0.014$), ASA physical status ($p = 0.001$), diabetes mellitus ($p = 0.002$), functional health status ($p<0.001$), pulmonary disease ($p = 0.004$), cardiovascular comorbidities ($p<0.001$), anemia ($p<0.001$), wound classification ($p = 0.045$), operative time ($p<0.001$), postoperative diagnosis ($p<0.001$), and surgery type ($p = 0.026$) (Table 4).

Results of the multivariable logistic regression analyses are outlined in Table 5. Risk factors of any postoperative complication included age ≥80 years, ASA physical statuses 3–5, partial or total dependence, pulmonary comorbidities, cardiovascular diseases, anemia, dirty/infected wounds, operative time ≥180 min, and postoperative diagnoses of meningiomas. Risk factors for infectious complications included age ≥80 years, ASA physical statuses 3–5, pulmonary comorbidities, dirty/infected wounds, and operative time ≥300 min. Those for non-infectious complications included age ≥80 years, partial or total functional dependence, cardiovascular diseases, anemia, operative time ≥180 min, and meningiomas. Lastly, risk factors for mortality included age ≥80 years, ASA physical statuses 3–5, partial or total dependence, disseminated cancer, anemia, and dirty/infected wounds.

Table 3
Multivariable logistic regression analyses for different 30-day postoperative complications with chronic steroid therapy as the main explanatory covariate.

Outcome	Adjusted odds ratio	P value
Any complication	1.481 [1.330–1.649]	<0.001
Infectious complications	1.522 [1.308–1.770]	<0.001
Surgical site infection	1.174 [0.909–1.517]	0.219
Superficial	1.122 [0.717–1.755]	0.615
Deep incisional	1.282 [0.738–2.229]	0.378
Organ/space	1.201 [0.835–1.728]	0.324
Urinary tract infection	1.687 [1.287–2.212]	<0.001
Sepsis	1.302 [0.938–1.806]	0.115
Septic shock	3.111 [1.952–4.957]	<0.001
Wound disruption	2.158 [1.060–4.393]	0.034
Pneumonia	1.579 [1.205–2.070]	0.001
Non-infectious complications	1.421 [1.256–1.609]	<0.001
CVA/stroke with neurological deficit	1.054 [0.775–1.434]	0.737
Cardiac complications	1.398 [0.876–2.230]	0.160
Myocardial infarction	0.804 [0.347–1.863]	0.611
Cardiac arrest requiring CPR	1.977 [1.150–3.397]	0.014
Pulmonary complications	1.351 [1.081–1.687]	0.008
Ventilator >48 h	1.369 [1.040–1.803]	0.025
Unplanned reintubation	1.314 [1.017–1.698]	0.037
Renal complications	0.950 [0.354–2.548]	0.918
Progressive renal insufficiency	0.602 [0.137–2.654]	0.503
Acute renal failure	1.306 [0.310–5.506]	0.716
Thromboembolism	1.767 [1.453–2.149]	<0.001
Pulmonary embolism	1.758 [1.317–2.348]	<0.001
DVT/Thrombophlebitis	1.756 [1.400–2.204]	<0.001
Blood transfusion	1.320 [1.084–1.607]	0.006
Unplanned reoperation	1.414 [1.200–1.666]	<0.001
Unplanned readmission	1.414 [1.265–1.581]	<0.001
Prolonged length of stay	0.955 [0.851–1.072]	0.436
Mortality	1.798 [1.376–2.349]	<0.001

No steroids group was reference; regression adjusted for age, gender, race, body mass index, smoking status, American Society of Anesthesiology physical status, diabetes mellitus, functional health status, pulmonary comorbidities, cardiovascular disease, renal disease, anemia, wound classification, operation time, postoperative diagnosis, and surgery type; only cases with complete data on all covariates and outcomes were included (N = 21,599); CVA: cerebrovascular accident; DVT: deep vein thrombosis.

4. Discussion

This study sought to explore the impact of steroid use for at least 10 days preoperatively on postoperative morbidity and mortality among patients undergoing craniotomy for tumor resection. In doing so, chronic steroid use was found to be significantly associated with most of the infectious and non-infectious complications studied in addition to unplanned reoperations, readmissions, and mortality. Our findings are congruent with published reports from other surgical disciplines (Ismael et al., 2011; White et al., 2019; Cloney et al., 2018). A multispecialty study reported increased risk of infectious complications and mortality among patients with steroid use (Ismael et al., 2011). In addition, these results also satisfy biological plausibility. Steroids are known to upregulate anti-inflammatory genes, such as interleukin 10 (IL-10) and glucocorticoid-induced leucine zipper (GILZ). In addition, steroids also

Table 4
Subgroup analysis of baseline characteristics, comorbidities, and operative variables stratified by postoperative complication status.

Variable	No complication N = 3635	At least 1 complication N = 751	P-value
Age/years*	58.0 (19.0)	61.0 (19.0)	<0.001
Age/years			
18 to 40	506 (13.9%)	90 (12.0%)	<0.001
41 to 60	1536 (42.3%)	262 (34.9%)	
61 to 80	1510 (41.6%)	359 (47.8%)	
More than 80	82 (2.3%)	40 (5.3%)	
Missing	1	0	
Gender			
Female	1924 (52.9%)	359 (47.8%)	0.010
Male	1710 (47.1%)	392 (52.2%)	
Missing	1	0	
Race			
White	2685 (89.7%)	522 (86.4%)	0.032
Black	188 (6.3%)	51 (8.4%)	
American Indian or Alaska Native	17 (0.6%)	1 (0.2%)	
Asian, Native Hawaiian, or Pacific Islander	104 (3.5%)	30 (5.0%)	
Missing	641	147	
BMI (kg/m^2)*	27.8 (7.6)	28.0 (7.6)	0.024
BMI (kg/m^2)			
Healthy (18.5 to <25)	1012 (28.2%)	174 (23.5%)	0.014
Underweight (<18.5)	71 (2.0%)	8 (1.1%)	
Overweight (25.0 to <30)	1247 (34.8%)	275 (37.1%)	
Obese (30 or higher)	1257 (35.0%)	284 (38.3%)	
Missing	48	10	
Current smoker	650 (17.9%)	124 (16.5%)	0.370
ASA classification			
ASA 1-2	791 (21.9%)	122 (16.3%)	0.001
ASA 3-5	2819 (78.1%)	625 (83.7%)	
Missing	25	4	
Diabetes mellitus	459 (12.6%)	127 (16.9%)	0.002
Functional health status			
Independent	3431 (94.8%)	674 (90.5%)	<0.001
Partially dependent	164 (4.5%)	58 (7.8%)	
Totally dependent	23 (0.6%)	13 (1.7%)	
Missing	17	6	
Pulmonary comorbidities	197 (5.4%)	61 (8.1%)	0.004
Cardiovascular disease	1337 (36.8%)	365 (48.6%)	<0.001
Renal disease	10 (0.3%)	4 (0.5%)	0.279
Anemia			
No	2768 (78.8%)	515 (70.0%)	<0.001
Yes	744 (21.2%)	221 (30.0%)	
Missing	123	15	
Wound classification			
Clean	3547 (97.6%)	728 (96.9%)	0.045
Clean contaminated	25 (0.7%)	5 (0.7%)	
Contaminated	54 (1.5%)	11 (1.5%)	
Dirty/infected	9 (0.2%)	7 (0.9%)	
Operative time/minutes*	190 (123)	220 (160)	<0.001
Operative time/minutes			
90 to 180	1653 (45.5%)	260 (34.6%)	<0.001
180 to <300	1365 (37.6%)	285 (37.9%)	
More than 300	617 (17.0%)	206 (27.4%)	
Postoperative diagnosis			
Intrinsic Brain Tumor	1640 (45.1%)	302 (40.2%)	<0.001
Meningioma	675 (18.6%)	200 (26.6%)	
Metastatic	1084 (29.8%)	179 (23.8%)	
Other Neoplasms	236 (6.5%)	70 (9.3%)	
Surgery type			
Supratentorial	3107 (85.5%)	618 (82.3%)	0.026
Infratentorial	528 (14.5%)	133 (17.7%)	

Only patients with chronic steroid therapy were included; * reported with median and interquartile range; percentages are presented in columns; BMI: body mass index; ASA: American Society of Anesthesiology; pulmonary comorbidities included ventilator dependence and chronic obstructive pulmonary disease; cardiovascular disease included hypertension requiring medications and congestive heart failure; renal disease included acute renal failure and preoperative dialysis.

downregulate pro-inflammatory genes, including nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) and activator protein 1 (AP-1)(Clark, 2007; Ayroldi and Riccardi, 2009; McKay and Cidlowski, 1999; Jonat et al., 1990). This disrupts the intricate balance of pro- and anti-inflammatory cytokines, resulting in impaired leukocyte chemotaxis, adhesion, and phagocytoses. The resulting immunosuppressive state may predispose patients to infections. This is especially concerning for patients undergoing craniotomy, considering the invasiveness of the procedure and long hospital stay duration which allow sufficient window for nosocomial infections.

In this study, steroid therapy was associated with 1.579 times increased odds of developing pneumonia. This is consistent with existing evidence reporting higher risk of pneumonia among patients with pulmonary comorbidities requiring steroid therapy (Thornton Snider et al., 2012; Lin et al., 2013). In addition to systemic immunosuppression, steroids are believed to have specific immunomodulatory impact on the pulmonary defense system. Steroid therapy reduces the number of alveolar macrophages which are responsible for antibody-dependent cellular cytotoxicity and antibacterial activity. Since alveolar macrophages are required for serving as the forefront of cellular defense and regulating immunity by T-helper cells type 2 (Th2), their dysfunction predisposes individuals to respiratory infections (Mathie et al., 2015).

Existing literature has associated steroid therapy with impaired diaphragm function, which can potentially lead to longer duration of postoperative mechanical ventilation. Steroids mediate this effect by facilitating diaphragm protein breakdown through lysosomal calpain and proteasomal proteases, resulting in impaired contractile strength and difficulties with weaning off ventilation (Sassoon et al., 2011). This can explain the higher odds of pulmonary complications among steroid group observed in this study.

Paradoxically, chronic steroid use in this study predisposed patients to both thromboembolic complications and blood transfusions. Bleeding leading to transfusions might be secondary to steroid-mediated changes to the coagulation process. These may include inhibited platelet aggregation, decreased fibrinogen levels, and increased antithrombin III levels and partial thrombin times (Narum et al., 2014). However, the prothrombotic effects of steroid are also documented, such as decreasing plasminogen and partial thromboplastin times and increasing factor VIII levels (Jørgensen et al., 1982). Due to these conflicting findings, the link between steroid therapy and hemostasis remains poorly understood.

In contrast to our findings, Alan et al. found no independent associations between chronic steroid therapy and postoperative complications among patients undergoing craniotomy for malignant tumor resection in both unmatched and propensity-score matched cohorts. The only exceptions were higher odds of readmissions and lower odds of prolonged length of stay among steroid group in the unmatched cohort (Alan et al., 2015). Our findings also contradict with earlier studies identifying steroid therapy as a risk factor of organ/space SSIs (Lieber et al., 2016; Merkler et al., 2014). No significant association was found between chronic steroid use and organ/space SSIs in this study. We speculate that these differences could potentially be attributed to changing disease and

Table 5
Multivariable logistic regression analysis of independent risk factors for mortality, any postoperative, infectious, and non-infectious complications in patients on preoperative steroid therapy undergoing craniotomy for brain tumor excisions.

Variable	Adjusted odds ratio	P-value
Any complication		
Age/years		
18 to 40	Reference	-
More than 80	2.418 [1.404–4.164]	0.001
ASA classification		
ASA 1-2	Reference	–
ASA 3-5	1.327 [1.021–1.726]	0.034
Functional health status		
Independent	Reference	–
Partially dependent	1.481 [1.011–2.169]	0.044
Totally dependent	3.219 [1.286–8.056]	0.012
Pulmonary comorbidities	1.592 [1.122–2.261]	0.009
Cardiovascular disease	1.310 [1.065–1.610]	0.011
Anemia	1.485 [1.201–1.837]	<0.001
Wound classification		
Clean	Reference	–
Dirty/infected	4.914 [1.600–15.094]	0.005
Operative time/minutes		
90 to 180	Reference	–
180 to <300	1.348 [1.083–1.678]	0.008
More than 300	2.173 [1.680–2.810]	<0.001
Postoperative diagnosis		
Intrinsic Brain Tumor	Reference	–
Meningioma	1.394 [1.084–1.792]	0.010
Infectious complications		
Age/years		
18 to 40	Reference	–
More than 80	2.686 [1.301–5.544]	0.008
ASA classification		
ASA 1-2	Reference	–
ASA 3-5	1.651 [1.108–2.461]	0.014
Pulmonary comorbidities	1.856 [1.196–2.882]	0.006
Wound classification		
Clean	Reference	–
Dirty/infected	6.720 [2.081–21.698]	0.001
Operative time/minutes		
90 to 180	Reference	–
More than 300	1.558 [1.085–2.238]	0.016
Non-infectious complications		
Age/years		
18 to 40	Reference	–
More than 80	2.227 [1.194–4.157]	0.012
Functional health status		
Independent	Reference	–
Partially dependent	1.847 [1.225–2.784]	0.003
Totally dependent	4.321 [1.651–11.309]	0.003
Cardiovascular disease	1.272 [1.001–1.616]	0.049
Anemia	1.780 [1.401–2.262]	<0.001
Operative time/minutes		
90 to 180	Reference	–
180 to <300	1.564 [1.207–2.026]	0.001
More than 300	2.665 [1.981–3.587]	<0.001
Postoperative diagnosis		
Intrinsic Brain Tumor	Reference	–
Meningioma	1.505 [1.130–2.004]	0.005
Mortality		
Age/years		
18 to 40	Reference	–
More than 80	4.037 [1.255–12.983]	0.019
ASA classification		
ASA 1-2	Reference	–
ASA 3-5	2.373 [1.006–5.600]	0.049
Functional health status		
Independent	Reference	–
Partially dependent	4.127 [2.311–7.369]	<0.001
Totally dependent	6.609 [1.796–24.326]	0.005
Disseminated cancer	2.397 [1.215–4.728]	0.012
Anemia	1.773 [1.126–2.791]	0.013
Wound classification		
Clean	Reference	–
Dirty/infected	5.788 [1.085–30.889]	0.040

Regression adjusted for age, gender, race, body mass index, American Society of Anesthesiology physical status, diabetes mellitus, functional health status, pulmonary comorbidities, cardiovascular disease, anemia, wound classification, operation time, postoperative diagnosis, and surgery type; only significant factors were reported; patients with chronic steroid therapy and with complete data on all covariates and outcomes were included (N = 3,418); ASA: American Society of Anesthesiology.

management paradigms over time. The earlier studies included patients who underwent craniotomy between 2005 and 2012 while our study included more recent patients.

Our subgroup analyses further revealed that older age, higher ASA physical statuses, functional dependence, pulmonary and cardiovascular comorbidities, anemia, dirty/infected wounds, prolonged operative time, disseminated cancer, and meningiomas further increased the risk of postoperative adverse events. These findings are in accord with previous studies across multiple surgical procedures (White et al., 2019; Cornellà et al., 2017; Kim et al., 2008).

There are several implications from this study. First, considering the ramifications associated with chronic steroid therapy, the need for reducing or even discontinuing steroid therapy as early as medically possible seems evident. However, since it may not be practical to reduce or stop preoperative steroids in certain patients, the feasibility, timing, and regimen for preoperative reduction or discontinuation of steroids should incorporate an individualized and multidisciplinary approach, involving medical and surgical providers in the decision-making process. It should be noted, however, that while the severity of side effects is linked with the dose and duration of steroid therapy(Dietrich et al., 2011), we cannot conclusively comment on whether preoperative reduction or cessation of therapy would reverse the associated risks. In addition, the time required for risk reversal after discontinuing or reducing steroids is further unknown. Further evidence is needed on these aspects to better inform clinical practice. Another important consideration is that outcomes of steroid therapy for peritumor edema were not explored in the current study, and our findings should not be extrapolated to such patients.

Second, understanding risk factors associated with morbidity and mortality among patients on chronic steroid therapy may help surgeons with preoperative planning and care optimization, potentially directing interventions to correct modifiable risk factors. While beyond the scope of the current study, pharmacological therapies might be beneficial in preoperative anemia management among patients on chronic steroid therapy (ASoATFoPB, 2015). The prospect of extended antimicrobial prophylaxis among patients on chronic steroid therapy undergoing craniotomy should be further evaluated, considering the higher incidence of infectious complications in this cohort. Existing guidelines mostly recommend the use of single-dose antimicrobial prophylaxis within 60 min of surgical incision for craniotomy patients (Bratzler et al., 2013). Duration, regimen, and timing of antimicrobial prophylaxis, however, were beyond the scope of the current study.

This study has multiple limitations which should be considered while interpreting our results. First, the ACS-NSQIP only records preoperative steroid use for patients receiving therapy for ≥10 days. Subsequently, patients who were on steroid therapy for a maximum of nine days would become part of the control group. This increases the likelihood that the impact of steroid therapy on postoperative morbidity and mortality is stronger than that observed in this analysis. Second, the regimen, dose, duration, and indication of steroid therapy were not explored, limiting the conclusiveness of the suggested clinical implications. Third, the analysis was restricted to variables captured in the ACS-NSQIP, and some variables that may influence postoperative complications could not be assessed. For instance, prior history of craniotomy is not documented in the database, but evidence suggests higher morbidity with repeated craniotomies (Hoover et al., 2013). Similarly, impact of postoperative steroid therapy could not be explored in the current study. Lastly, the dataset involves manual data entry and is susceptible to errors during data collection and coding.

5. Conclusion

Preoperative brain tumor patients on steroids for 10 or more days are at a relatively high risk of postoperative complications. We recommend a judicious use of steroids in brain tumor patients undergoing craniotomy, both in terms of dosage and duration of treatment. Given the associated risks, the need to reduce or even discontinue steroids as early before surgery as medically possible seems appropriate. Additionally, optimized care should be provided to patients on chronic steroid therapy, and efforts should be made to prevent associated morbidity.

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Data statement

Data acquired was obtained through the ACS-NSQIP database and is used with the permission of The American College of Surgeons.

Disclaimer

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bas.2023.101725.

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