Journal of Clinical Neuroscience 81 (2020) 95–100

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Clinical study

Frailty and outcomes after craniotomy for brain tumor

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ARTICLE INFO

Article history:
Received 20 July 2020
Accepted 6 September 2020

Keywords:
Neurosurgery
Geriatrics
Complications
Glioma
Meningioma
Risk stratification

ABSTRACT

Frailty has been associated with increased morbidity and mortality in a variety of surgical disciplines. Few data exist regarding the relationship of frailty with adverse outcomes in craniotomy for brain tumor resection. We assessed the relationship between frailty and the incidence of major post-operative complication, discharge destination other than home, 30-day readmission, and 30-day mortality after elective craniotomy for brain tumor resection. A retrospective cohort study was conducted on 20,333 adult patients undergoing elective craniotomy for tumor resection in the 2012–2018 ACS-NSQIP Participant Use File. Multivariate logistic regression was performed using all covariates deemed eligible through clinical and statistical significance. 6,249 patients (30.7%) were low-frailty and 2,148 patients (10.6%) were medium-to-high frailty. In multivariate logistic regression adjusting for age, gender, BMI, ASA classification, smoking status, dyspnea, significant pre-operative weight loss, chronic steroid use, bleeding disorder, tumor type, and operative time, low frailty was associated with increased adjusted odds ratio of major complication (1.41, 95% CI: 1.23–1.60, $p < 0.001$), discharge destination other than home (1.32, 95% CI: 1.20–1.46, $p < 0.001$), 30-day readmission (1.29, 95% CI: 1.15–1.44, $p < 0.001$), and 30-day mortality (1.87, 95% CI: 1.41–2.47, $p < 0.001$). Moderate-to-high frailty was also associated with increased adjusted odds of major complication (1.61, 95% CI: 1.35–1.92, $p < 0.001$), discharge destination other than home (1.80, 95% CI: 1.58–2.05), 30-day readmission (1.39, 95% CI: 1.19–1.62, $p < 0.001$), and 30-day mortality (2.42, 95% CI: 1.74–3.38, $p < 0.001$).

Conclusions: Frailty is associated with increased odds of major post-operative complication, discharge to destination other than home, 30-day readmission, and 30-day mortality.

1. Introduction

As the population ages, the incidence of primary and metastatic intracranial tumors has increased [1]. Identification of risk factors that place surgical candidates at elevated risk of peri-operative morbidity or mortality is imperative for informed surgical decision-making. Research suggests that age alone is a weak predictor of adverse outcomes in patients undergoing craniotomy for brain tumors [2]. Excess frailty is defined as a progressive and cumulative decline in physiologic reserve, which may reflect increased vulnerability to stressors [3]. Frailty has been shown to correlate with increased risk of complication, readmission, and mortality after both inpatient and outpatient surgery in multiple surgical disciplines either independent of, or superior to, age alone [4–11]. Although data regarding intracranial tumor resection is considerably more limited, both small, institutional cohorts and larger, retrospective database analyses have suggested a link between increasing frailty and morbidity and mortality [12–17]. Standards of neuro-oncologic care for both primary and metastatic tumors to the brain have evolved, however, and these analyses must be updated to reflect contemporary practice [18,19].

Numerous indices, such as the Hopkins Frailty Score, modified frailty index, and the risk analysis index (RAI), have been developed to quantify frailty. Youngerman *et al* used the original modified frailty index (mFI-11), an 11-factor score developed by the American College of Surgeons National Surgical Quality Improvement Program (NSQIP), to assess rates of adverse outcomes in a cohort of 9,149 patients derived from the 2008–2012 NSQIP databases. Utility of mFI-11, while correlated with morbidity and mortality in this and other contexts, has been limited by post-2012 changes to NSQIP, which now only reports a subset of the original 11 variables [20]. Although mFI-11 continues to be used in retro-

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https://doi.org/10.1016/j.jocn.2020.09.002
0967-5868/

spective surgical research, the lack of complete data for all composite variables limits conclusions that can now be drawn from contemporary analyses [21]. A new, 5-factor modified frailty index (mFI-5), which measures the presence of congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), dependent functional status, diabetes, and hypertension, has been shown to be equally effective as the mFI-11 in quantifying frailty and predicting morbidity and mortality in studies outside neurosurgery [20]. We assessed the relationship between frailty, as determined by mFI-5, and outcomes after elective craniotomy for intracranial neoplasms.

2. Methods

2.1. Patient characteristics

Data were obtained from the 2012–2018 NSQIP participant use file (PUF). NSQIP is a Health Insurance Portability and Accountability Act (HIPAA)-compliant data file; it contains patient-level, aggregate data and does not identify patients, hospitals, or providers. Therefore, this study was deemed exempt from review by the Institutional Review Board of [BLINDED FOR REVIEW]. As this study utilized a de-identified national database, informed consent was not required.

We analyzed adult (age $\geq$ 18 years) patients undergoing elective cranial surgery for tumor. We identified patients through a combination of Current Procedural Terminology (CPT) and post-operative International Classification of Disease (ICD) codes (see Supplementary Table 1). Inclusion and exclusion criteria were designed to select for the most medically-optimized patient population we could reasonably achieve using NSQIP.

We excluded patients who underwent non-elective surgery, as identified by the elective surgery variable, the emergency surgery variable, and the most severe American Society of Anesthesiologists (ASA) classes (greater than ASA IV; see below). Patients were included only if they arrived from their home on the day of surgery to avoid elevated rates of infection from sites outside the home and contamination associated with hospital environments [22,23]. We excluded patients who were pregnant or in the puerperium period, patients who received preoperative blood transfusions, and patients with an infection present at the time of surgery, which are associated with increased peri-operative morbidity. Finally, we excluded patients with hospital stays of <2 days, to focus the analysis on major surgery and exclude minor procedures or patients admitted for observation or extended recovery. 20,333 patients remained after these exclusion criteria were applied, as summarized in Fig. 1.

mFI-5 and Outcomes: The mFI-5 score was calculated by adding the number of present variables for a given patient and dividing by 5. Scores were then classified as non-frailty (mFI-5 = 0), low frailty (mFI = 0.2), or medium-to-high frailty (mFI > 0.2), in concordance with other studies that have used mFI-5 [11,24,25].

We compared characteristics including patient demographics, comorbidities, and operative factors between the baseline (mFI-5 = 0) group and the low and medium–high frailty groups. Covariates were included based on clinical relevance, prior studies of outcomes in cranial surgery, and availability in NSQIP, and are summarized in Table 1. Tumors were categorized into meningioma, intrinsic brain tumor, metastatic disease, and other. The "other" category consists of mostly cranial nerve tumors, neoplastic vascular lesions, and unspecified tumors (data not shown). All covariates have <1% missing data except for race, which is missing approximately 20% of observations.

The primary outcome of this study was post-operative major complication within 30 days of surgery. Major complication was defined as one or more of deep incisional surgical site infection, organ or space surgical site infection, wound disruption, pneumonia, sepsis or septic shock, unplanned intubation, pulmonary embolism, >48-hour postoperative ventilator-assisted respiration, progressive renal insufficiency, acute renal failure, cardiovascular accident with neurological deficit, coma of >24 h, peripheral nerve injury, cardiac arrest requiring cardiopulmonary resuscitation, myocardial infarction, graft, and prosthesis or flap failure. Secondary outcomes were discharge destination other than home, 30-day readmission, and 30-day mortality.

2.2. Statistical methods

Patient demographics, comorbidities, and operative factors were compared between the control and each frailty cohort using the Pearson χ^2 test for categorical variables and Student's *t*-test for continuous variables. To identify the relationship of frailty status with each outcome, multivariate logistic regression was performed using all covariates deemed eligible through clinical relevance and statistical significance. To avoid over-estimation of significance and other sources of bias, variable selection methods were not used [26]. Final outcomes models were adjusted for age (considered a continuous variable), gender, BMI (categorized as < 18.5, 18.5–25, 25.1–30.0, >30.0), ASA classification (categorized as I-II, III, and IV), smoking status, dyspnea, significant weight loss, chronic steroid use, bleeding disorder, and operative time. As there are >10 patients per included variable, the model is not at risk of being overfit [26]. Excluded covariates included ascites, renal failure, and dialysis due to insufficient numbers to reduce model overfitting; disseminated cancer, due to significant correlation with the metastatic disease tumor category; and race, due to significant missing data. Sensitivity analyses demonstrated that the inclusion of race did not significantly affect the risks associated with our variables of interest (data not shown).

In our models, frailty was included as a three-level variable with odds ratios reported in relation to the "No Frailty" group. We also report odds ratios for tumor types, with meningioma as the reference group due to lower anticipated risks associated with surgery for extra-axial tumor. All outcomes regressions were assessed for goodness-of-fit using Pearson χ^2 and all were significant ($p < 0.05$). No attempt was made to optimize the models for predictive power using stepwise regression or other methods. For all analyses, a p-value of $\leq$0.05 was considered significant. Stata, version 16 (StataCorp LP, College Station, Texas), was used.

3. Results

We analyzed a cohort of 20,333 patients who underwent elective craniotomy for intracranial tumor resection. Baseline demographic and comorbidity data for all included patients are summarized in Table 1**.** 6,249 patients (30.7%) were low-frailty and 2,148 patients (10.6%) were medium-to-high frailty. The overall distribution of mFI-5 scores in the studied population is summarized in Table 2. Both low- and medium-to-high-frailty patient groups were older than the non-frailty patient group and were more likely to be male (45.75% and 50.61% vs 42.31%), non-white (14.49% and 18.80% vs 10.25%), and obese (45.38% and 54.70% vs 30.71%). They were also more likely to have a higher ASA classification (although >50% in all three groups were noted to be ASA 3 +) and to have history of smoking, dyspnea, disseminated cancer, chronic steroid use, and bleeding disorders. Medium-to-high frailty patients also had a significantly higher rate of significant weight loss (1.63% vs 0.90%) as compared to the non-frailty patients; however, the same trend, while present, was not found to be statistically significant for low-frailty patients. Data for patients with ascites, renal failure, and need for dialysis did

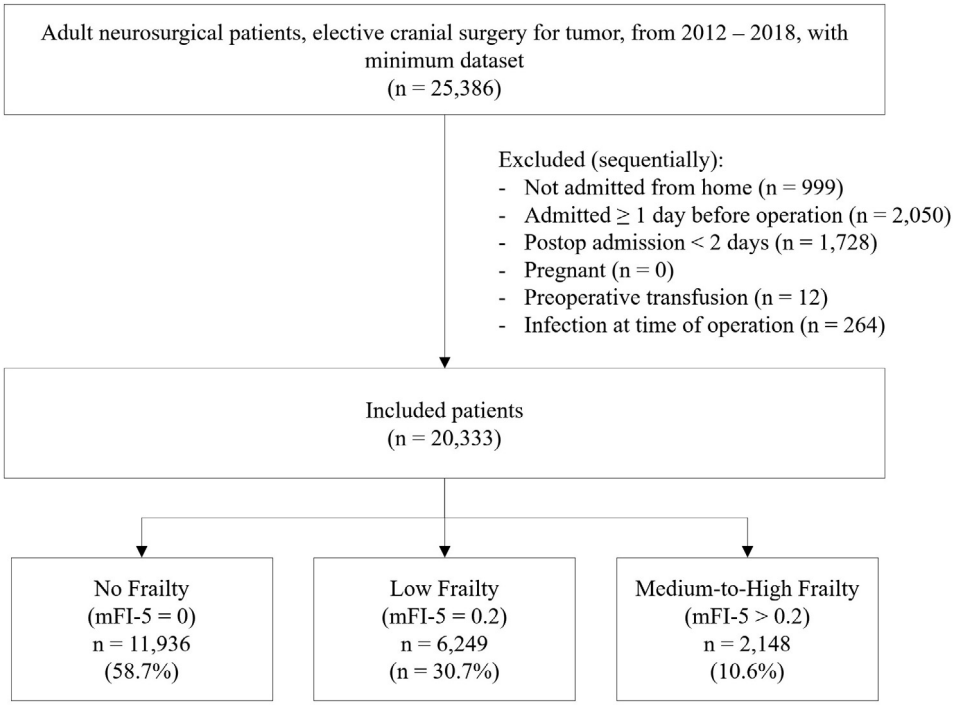

Fig. 1. Population selection diagram.

Table 1
Demographic, comorbidity, and operative factors for different frailty groups; comparisons made with the baseline group (no frailty).

Characteristic	Entire population N = 20,333	No frailty (mFI-5 = 0) N = 11,936	Low frailty (mFI-5 = 0.2) N = 6,249	P-values	Medium-to-high frailty (mFI-5 > 0.2) N = 2,148	P-values
Mean age, years (SD)	54.85 (12.11)	49.48 (14.83)	61.69 (12.24)	**<0.001**	64.77 (10.46)	**<0.001**
Age distribution, years (%)				**<0.001**		**<0.001**
18–65	14,431 (70.97%)	9,945 (83.32%)	3,521 (56.35%)		965 (44.93%)	
65–74	4,208 (20.70%)	1,558 (13.05%)	1,837 (29.40%)		813 (37.85%)	
75+	1,694 (8.33%)	433 (3.63%)	891 (14.26%)		370 (17.23%)	
Gender, male (%)	8,996 (44.24%)	5,050 (42.31%)	2,859 (45.75%)	**<0.001**	1,087 (50.61%)	**<0.001**
Race, not-white (%)		947 (10.25%)	746 (14.49%)	**<0.001**	335 (18.80%)	**<0.001**
BMI (%)				**<0.001**		**<0.001**
<18.5	289 (1.43%)	210 (1.77%)	59 (0.95%)		20 (0.94%)	
18.5–25.0	5,400 (26.75%)	3,906 (32.97%)	1,166 (18.76%)		328 (15.43%)	
25.1–30.0	6,879 (34.07%)	4,093 (34.55%)	2,171 (34.92%)		615 (28.93%)	
>30.0	7,622 (37.75)	3,638 (30.71%)	2,821 (45.38%)		1,163 (54.70%)	
ASA Classification (%)				**<0.001**		**<0.001**
1 & 2	6,690 (32.90%)	5,073 (42.50%)	1,412 (22.60%)		205 (9.54%)	
3	12,213 (60.06%)	6,284 (52.65%)	4,319 (69.12%)		1,610 (74.95%)	
4	1,430 (7.03%)	579 (4.85%)	518 (8.29%)		333 (15.50%)	
Comorbidities						
Smoker	3,047 (14.99%)	1,808 (15.15%)	878 (14.05%)	**0.048**	361 (16.81%)	**0.049**
Obese BMI > 30	7,622 (37.75)	3,638 (30.71%)	2,821 (45.38%)	**<0.001**	1,163 (54.70%)	**<0.001**
Dyspnea	771 (3.79%)	226 (1.89%)	322 (5.15%)	**<0.001**	223 (10.38%)	**<0.001**
Ascites	4 (0.02%)	3 (0.03%)	1 (0.02%)	–[†]	0 (0.00%)	–[†]
Renal Failure	1 (<0.01%)	0 (0.00%)	1 (0.02%)	–[†]	0 (0.00%)	–[†]
Dialysis	22 (0.11%)	4 (0.03%)	9 (0.14%)	–[†]	9 (0.42%)	–[†]
Disseminated Cancer	2,811 (13.82%)	1,368 (11.46%)	982 (15.71%)	**<0.001**	461 (21.46%)	**<0.001**
Chronic Steroid Use	3,296 (16.21%)	1,746 (14.63%)	1,115 (17.84%)	**<0.001**	435 (20.25%)	**<0.001**
Significant weight loss	209 (1.03%)	108 (0.90%)	66 (1.06%)	0.319	35 (1.63%)	**0.002**
Bleeding disorder	253 (1.24%)	96 (0.80%)	106 (1.70%)	**<0.001**	51 (2.37%)	**<0.001**
Tumor Type				**<0.001**		**<0.001**
Intrinsic brain tumor	8,371 (41.17%)	5,461 (45.75%)	2,252 (36.04%)		658 (30.63%)	
Meningioma	6,197 (30.48%)	3,264 (27.35%)	2,148 (34.37%)		785 (36.55%)	
Metastatic disease	2,651 (13.04%)	1,269 (10.63%)	950 (15.20%)		432 (20.11%)	
Other neoplastic condition	3,114 (15.32%)	1,942 (16.27%)	899 (14.39%)		273 (12.71%)	
Mean operative time, minutes (SD)	234.1 (138.81)	241.45 (141.25)	226.61 (135.51)	**<0.001**	215.00 (131.45)	**<0.001**

ASA = American Society of Anesthesiologists, BMI = Body Mass Index, SD = Standard Deviation.
Student's T-test used to compare continuous variables and Pearson's χ^2 used to compare categorical variables.
[†] Group sizes inadequate to calculate χ^2 statistic, which requires ≥ 5 per group.

Table 2
Incidence of mFI-5 qualifying comorbidities in each mFI-5 group.

mFI-5 qualifying condition	No frailty (mFI-5 = 0) N = 11,936	Low frailty (mFI-5 = 0.2) N = 6,249	Medium-to-high frailty (mFI-5 > 0.2) N = 2,148
Congestive heart failure	–	0.08%	1.49%
Chronic obstructive pulmonary disease	–	3.58%	18.67%
Dependent functional status	–	3.20%	11.82%
Diabetes	–	8.58%	79.80%
Hypertension	–	84.56%	97.49%

not meet the minimum patient number (5) to allow for analysis with the χ^2 test. Both low- and medium-to-high-frailty patients were found to have shorter operative times (226.61 min and 215.00 min vs 241.45 min) than the non-frailty patients. The incidences of comorbidities used in the mFI-5 score are summarized in Supplementary Table 2**.** 84.56% and 97.49%, respectively, of low- and medium-to-high-frailty patients were positive for hypertension. Substantially larger numbers of medium-to-high-frailty patients were positive for CHF (1.49% vs 0.08%), COPD (18.67% vs 3.58%), dependent functional status (11.82% vs 3.20%), and diabetes (79.80% vs 8.58%).

The incidence of the adverse outcomes included in this analysis in both low- and medium-to-high-frailty cohorts are summarized in Table 3**.** Increasing incidence of all studied outcomes were noted in the low-frailty cohort relative to the no-frailty cohort and in the medium-to-high-frailty cohort.

The results of multivariate analysis are summarized in Table 4**.** When adjusting for other covariates, we found statistically-significant associations between major complications and both low (adjusted OR 1.41) and medium-to-high mFI-5 scores (adjusted OR 1.61), although the confidence intervals for these covariates overlap. A similar, statistically-significant association was found for discharge to destination other than home (adjusted OR 1.32 and 1.80), 30-day readmission (adjusted OR 1.29 and 1.39), and 30-day mortality (adjusted OR 1.87 and 2.42). Medium-to-high mFI-5 scores had statistically significant association with 30-day mortality even when compared to low frailty.

Tumor type was not associated with increased risk of major complication in this multivariate analysis relative to the control cohort of meningioma. Intrinsic brain tumor was associated with an increased risk of discharge destination other than home (adjusted OR 1.29), 30-day readmission (adjusted OR 1.18), and 30-day mortality (adjusted OR 1.81). Metastatic brain tumors were associated with increased risks of both 30-day readmission (adjusted OR 1.47) and 30-day mortality (adjusted OR 2.61) but not of discharge destination other than home. Other tumor type was only associated with an increased risk of 30-day readmission (adjusted OR 1.32). The full results of multivariate analysis for severe complication can be found in Supplementary Table 3**.**

4. Discussion

Understanding factors that may increase the likelihood of adverse outcomes is essential to inform surgical decision-making and improve the process of informed consent, which, for elderly patients undergoing major surgery, may be suboptimal [27]. Although factors such as major post-operative complications, unplanned readmissions, and mortality are intrinsically meaningful for patients and their families, it is also true that, in the context of oncologic care, major post-operative complications can delay adjuvant therapy and carry an independent survival cost to patients [28,29]. It is unclear whether frail patients, who have a higher risk of *peri*-operative complications, would benefit from targeted *peri*-operative integrated care protocols and/or prehabilitation, as has been discussed in other surgical fields [30].

Our results demonstrate that, when controlling for relevant covariates, increasing frailty is associated with increased risk of major complication, discharge destination other than home, 30-day readmission, and 30-day mortality. There was a trend toward increased risk of all studied adverse outcomes with increasing frailty, though this trend was only noted to be significant for 30-day readmissions. The overall incidence of these adverse outcomes is not trivial in our population. Multivariate analysis suggests that, for example, low- and medium-to-high-frailty status confer nearly 2- and 2.5-times increased odds of mortality when compared to non-frail patients. Varied tumor types have mixed effects with regards to these adverse outcomes; for example, metastatic tumors were associated with no significant increase in immediate post-operative outcomes (major complication, discharge destination) but was associated with significant increase in likelihood of delayed post-operative outcomes (30-day readmission and mortality).

Our results extend Youngerman's results, in a much larger and more contemporaneous patient population [17]. Although their analysis used mFI-11 in a pre-2012 population, the 3 most prevalent constituent medical conditions they analyzed – hypertension, diabetes, and dependent functional status – are well represented in mFI-5 [17]. While mFI-5 is a simpler measure of frailty, our analysis is evidence that plain, objective measures of pre-operative risk can identify patients at increased risk of important adverse post-operative outcomes. Furthermore, we excluded patients who underwent transsphenoidal tumor resections, who made up 7.3% of patients in Youngerman et al and were not found to have significant associations with any adverse outcomes other than unfavorable discharge destination [17].

A variety of models exist to quantify frailty. Generally, these metrics can be divided into phenotype models and cumulative deficit models, of which mFI-5 is one example [3]. The results of our analysis are broadly in concordance with analyses of both subtypes of frailty metrics [12,13,16]. ASA class and Karnofsky Performance Score (KPS), both of which are commonly used in neurosurgical oncology for risk stratification, are more phenotypic measures of resilience; however, both are inherently subjective assessments of health and functional status with more limited utility in surgical prognostication. Regardless, the existing literature regarding *peri*-operative prediction in cranial neurosurgery remains limited [31].

Our study has limitations. NSQIP contains only data on patients who had surgery. One cannot account for variation in surgeon or hospital volume, critical care resources, experience, or socioeconomic factors such as hospital type or insurance status. NSQIP does not detail the reason for re-admission or re-operation. It is possible that the surgical population captured is not wholly representative of the US patient population, but at 700 + hospitals, with a 60:40 split between academic and non-academic institutions (data not shown), these results may be a reasonable reflection. NSQIP data is collected prospectively in a standardized and audited manner, from a variety of institutions which has been shown, in most surgical specialties to be a robust reflection of the US population [32,33]. Additionally, the available variables, while large, diverse, and more robust than other national databases, do preclude utilization of other cumulative deficit models of frailty, such as mFI-11, and all subjective models of frailty. Outcomes are constrained to the period of 30 days from the index operation. Available data do not allow us to assess factors associated with long-term functional decline and loss of independence. Future studies could seek

Table 3
Incidence of outcomes across frailty cohorts.

Outcome	Entire population	No frailty (mFI-5 = 0)	Low frailty (mFI-5 = 0.2)	Medium-to-high frailty (mFI-5 > 0.2)
Major Complication	7.00%	5.24%	8.93%	11.17%
Discharged not to home	14.96%	10.92%	19.00%	25.85%
30-day readmission	10.22%	8.77%	11.88%	13.46%
30-day mortality	1.64%	0.83%	2.38%	3.96%

Table 4
Associated risks of frailty and tumor type from multivariate logistic regression models on outcomes after cranial surgery for tumor.

Outcome	aOR[1]	95% CI	p-value	c-statistic
Major complication				0.681
Frailty (mFI-5)				
No Frailty (mFI-5 = 0)	Ref			
Low Frailty (mFI-5 = 0.2)	1.41	1.23–1.60	**<0.001**	
Medium-High Frailty (mFI-5 > 0.2)	1.61	1.35–1.92	**<0.001**	
Tumor Type				
Meningioma	Ref			
Intrinsic Brain	1.03	0.89–1.18	0.696	
Metastatic disease	0.88	0.73–1.08	0.218	
Other	0.87	0.73–1.04	0.128	
Discharged not to home				0.704
Frailty (mFI-5)				
No Frailty (mFI-5 = 0)	Ref			
Low Frailty (mFI-5 = 0.2)	1.32	1.20–1.46	**<0.001**	
Medium-High Frailty (mFI-5 > 0.2)	1.80	1.58–2.05	**<0.001**	
Tumor Type				
Meningioma	Ref			
Intrinsic Brain	1.29	1.17–1.42	**<0.001**	
Metastatic disease	0.78	0.67–0.90	**0.001**	
Other	0.78	0.68–0.90	**<0.001**	
30-day readmission				0.601
Frailty (mFI-5)				
No Frailty (mFI-5 = 0)	Ref			
Low Frailty (mFI-5 = 0.2)	1.29	1.15–1.44	**<0.001**	
Medium-High Frailty (mFI-5 > 0.2)	1.39	1.19–1.62	**<0.001**	
Tumor Type				
Meningioma	Ref			
Intrinsic Brain	1.18	1.04–1.33	**0.009**	
Metastatic disease	1.47	1.26–1.71	**<0.001**	
Other	1.32	1.14–1.53	**<0.001**	
30-day mortality				0.786
Frailty (mFI-5)				
No Frailty (mFI-5 = 0)	Ref			
Low Frailty (mFI-5 = 0.2)	1.87	1.41–2.47	**<0.001**	
Medium-High Frailty (mFI-5 > 0.2)	2.42	1.74–3.38	**<0.001**	
Tumor Type				
Meningioma	Ref			
Intrinsic Brain	1.81	1.31–2.48	**<0.001**	
Metastatic disease	2.61	1.84–3.71	**<0.001**	
Other	0.95	0.59–1.53	0.848	

aOR = Adjusted Odds Ratio, CI = Confidence Interval.
Significant p-values ($p < 0.05$) in bold.
[1] Full models adjusting for all eligible covariates from Table 1 including: age, gender, BMI category, ASA classification, smoking status, dyspnea, significant weight loss, chronic steroid use, bleeding disorder, and operative time.

to prospectively evaluate both phenotypic and cumulative deficit models of frailty with greater attention paid to medium- and long-term outcomes after craniotomy for tumor resection. Such results should motivate a commensurate improvement in pre-operative prognostication tools and prompt modification of both pre-operative discussions with patients as well as in *peri*-operative care protocols for patients identified to be at increased risk of *peri*-operative complications.

5. Conclusions

Pre-operative frailty, as determined by mFI-5, is associated with substantially increased odds of major post-operative complication, discharge to a destination other than home, 30-day readmission, and 30-day mortality. These results should encourage increased attention to pre-operative indicators of frailty in patients having cranial neurosurgery for tumor resection. Further work will be necessary to establish the relative discriminatory ability of each frailty metric and determine the long-term consequences of surgery in frail patients.

6. Authorship

Conceived and Designed the Study: RS, NJP, BS, RJW
Access to the full and complete data set: NJP, RJW
Analyzed the data: All authors
Performed the statistical analyses: NJP, OT, BS, RS
Wrote the paper: RS, NJP, RJW
Critically revised the manuscript: All authors
Reviewed and approved the final manuscript: All authors

Funding

NJP was supported, in part, by a Ruth Sauber Medical Scholar Award from the Warren Alpert School of Medicine at Brown University. The funders of this philanthropic support had no role in the study.

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.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jocn.2020.09.002.

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