The 5-factor modified frailty index: an effective predictor of mortality in brain tumor patients

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OBJECTIVE Health measures such as the Charlson Comorbidity Index (CCI) and the 11-factor modified frailty index (mFI-11) have been employed to predict general medical and surgical mortality, but their clinical utility is limited by the requirement for a large number of data points, some of which overlap or require data that may be unavailable in large datasets. A more streamlined 5-factor modified frailty index (mFI-5) was recently developed to overcome these barriers, but it has not been widely tested in neuro-oncology patient populations. The authors compared the utility of the mFI-5 to that of the CCI and the mFI-11 in predicting postoperative mortality in brain tumor patients.

METHODS The authors retrospectively reviewed a cohort of adult patients from a single institution who underwent brain tumor surgery during the period from January 2017 to December 2018. Logistic regression models were used to quantify the associations between health measure scores and postoperative mortality after adjusting for patient age, race, ethnicity, sex, marital status, and diagnosis. Results were considered statistically significant at p values ≤ 0.05. Receiver operating characteristic (ROC) curves were used to examine the relationships between CCI, mFI-11, and mFI-5 and mortality, and DeLong's test was used to test for significant differences between c-statistics. Spearman's rho was used to quantify correlations between indices.

RESULTS The study cohort included 1692 patients (mean age 55.5 years; mean CCI, mFI-11, and mFI-5 scores 2.49, 1.05, and 0.80, respectively). Each 1-point increase in mFI-11 (OR 4.19, p = 0.0043) and mFI-5 (OR 2.56, p = 0.018) scores independently predicted greater odds of 90-day postoperative mortality. Adjusted CCI, mFI-11, and mFI-5 ROC curves demonstrated c-statistics of 0.86 (CI 0.82–0.90), 0.87 (CI 0.83–0.91), and 0.87 (CI 0.83–0.91), respectively, and there was no significant difference between the c-statistics of the adjusted CCI and the adjusted mFI-5 models (p = 0.089) or between the adjusted mFI-11 and the adjusted mFI-5 models (p = 0.82). The 3 indices were well correlated (p < 0.01).

CONCLUSIONS The adjusted mFI-5 model predicts 90-day postoperative mortality among brain tumor patients as well as our adjusted CCI and adjusted mFI-11 models. The simplified mFI-5 may be easily integrated into clinical workflows to predict brain tumor surgery outcomes in real time.

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KEYWORDS frailty; oncology; outcomes

Aമ്MPLE research has been directed toward developing methods of predicting mortality and other outcomes among patients based upon existing comorbidities and other factors, including age and functional status.[1–13] This line of investigation has led to the development of frailty indices, which relate accrued deficits and comorbidities in patients to risks of short- and long-term complications and death.[11]

The Charlson Comorbidity Index (CCI) and 11-factor modified frailty index (mFI-11) are well-validated health measures that have been applied within general medical and surgical datasets to retrospectively stratify patients based on their risks for the development of posttreatment complications and mortality.[1–17] Use of these measures requires eliciting specific patient history elements and assigning associated point values to each element in order to generate a composite score. Created in 1987 by Mary E. Charlson, the CCI incorporates the use of 19 separate health conditions on a 1- to 6-point scale (minimum score 0, maximum score 37) to develop a composite score (Table

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TABLE 1. Comparison of the components of the CCI, mFI-11, and mFI-5

CCI (score weight)	mFI-11	mFI-5
AIDS (6)	Functional status*	Functional status*
Metastatic solid tumor (6)	History of diabetes	History of diabetes
Moderate or severe liver disease (3)	Respiratory problems	History of COPD
Lymphoma (2)	Congestive heart failure	Congestive heart failure
Leukemia (2)	Arterial hypertension	Hypertension
Any tumor (2)	Cardiac problems	—
Diabetes with end-organ damage (2)	Myocardial infarction	—
Moderate or severe renal disease (2)	Delirium	—
Hemiplegia (2)	History related to cognitive impairment or loss	—
Diabetes (1)	Cerebrovascular problems	—
Mild liver disease (1)	History of stroke or decreased peripheral pulses	—
Ulcer disease (1)	—	—
Connective tissue disease (1)	—	—
Chronic pulmonary disease (1)	—	—
Dementia (1)	—	—
Cerebrovascular disease (1)	—	—
Peripheral vascular disease (1)	—	—
Congestive heart failure (1)	—	—
Myocardial infarction (1)	—	—
Age (+1 each decade ≥50 yrs)	—	—

* Functional status score: 1 = requiring assistance with activities of daily living; 0 = not requiring assistance.

1). For example, "diabetes with end-organ damage" and "hemiplegia" are each assigned 2 points within the CCI scoring system.[18]

The mFI-11 was created in 2012 in an attempt to create a more simplified risk stratification tool. In contrast to the CCI, each element of the mFI-11 accounts for only 1 point. Additionally, the mFI-11 includes some physical examination findings, such as "decreased peripheral pulses." Furthermore, several elements within the mFI-11 seemingly clinically overlap, including "respiratory problems" with "congestive heart failure," "cardiac problems" with "myocardial infarction," and "delirium" with "history related to cognitive impairment or loss" (Table 1).

Although these indices have demonstrated promising utility for clinical use, it remains time-consuming to elicit the necessary data elements in real time, and calculations of weighted elements specifically for the CCI are not intuitive or expeditious in the clinical setting. As a result, there has been limited clinical adoption of these tools, which has promoted increasing interest in creating and validating a simple, clinic-friendly tool capable of predicting important posttreatment outcomes in surgical patients.

In an attempt to address this need for a simpler health measurement tool, the simplified 5-factor modified frailty index (mFI-5) was recently introduced and validated within the general surgery literature.[6] The mFI-5 includes 5 nonoverlapping clinical conditions, namely functional status, history of diabetes, history of chronic obstructive pulmonary disease, congestive heart failure, and hypertension, which are all characterized during routine clinic visits. Each condition is assigned a 1-point value, for a minimum score of 0 and a maximum score of 5. Importantly, this tool does not include any physical examination elements. An mFI-5 score ≥ 1 has been associated with high rates of patient morbidity and mortality in the surgical literature.[2,7]

The primary goal of this study was to perform what was to our knowledge the first comparative analysis of the predictive capabilities of the CCI, mFI-11, and mFI-5 in brain tumor patients. Identifying a small subset of preoperative factors significantly correlated with short- and longer-term outcomes vis-à-vis the mFI-5 may be clinically useful to help risk stratify those primary brain tumor patients for whom neurosurgical intervention is being considered.

Methods

Patient Selection and Recorded Variables

We conducted our study using a cohort of 1925 adult (age ≥ 18 years) patients who were operated on for brain tumors at a single institution between January 1, 2017, and December 31, 2018. After only including cases in which patients were undergoing their first brain tumor surgery (repeat surgeries were excluded), our cohort size decreased to 1692 patients. Our IRB, acting as a HIPAA Privacy Board, reviewed and approved the waiver of informed consent for this retrospective, HIPAA-compliant study (IRB00209855). Variables collected for this study by the Center for Clinical Data Analysis at our institution included patient age, race and ethnicity, sex, marital status, and mortality. Each patient's diagnosis and preoperative

Karnofsky Performance Status (KPS) score were verified using manual chart review of electronic health records (EHRs).

CCI, mFI-11, and mFI-5 scores were calculated for each patient. There were no patients in our cohort who had missing medical comorbidity data, and therefore we were able to calculate CCI, mFI-5, and mFI-5 scores for all 1692 patients. Table 1 displays the various factors comprising the CCI, mFI-11, and mFI-5. We derived these factors from a clinical institutional database created using the ICD-10 codes, which were extracted from the EHR system. Notably, the CCI scores were calculated as a weighted index (1–6 points), meaning that specific comorbidities (e.g., AIDS or metastatic solid tumor) contribute more to the final value of the index. In contrast, for each factor within the mFI-11 and mFI-5, a score of 1 indicates that the patient has the comorbidity and a score of 0 indicates the patient does not have the comorbidity. For functional status, 0 was defined as requiring no assistance with daily living and 1 was defined as requiring any assistance.[6] A total score was obtained for each index by summation of these numbers. Patients were stratified according to the median CCI, mFI-11, and mFI-5 scores. In this study, 90-day postoperative mortality was defined as any patient death within 90 days of the initial hospital admission associated with surgery.

Statistical Analysis

Statistical analyses were conducted using SPSS version 25 (IBM Corp.). Fisher's exact test was used for bivariate analysis of categorical variables, the independent-samples t-test was used to compare continuous variables, and Levene's test was used to compare the variance of continuous variables calculated for 2 groups. Spearman's rho was used to quantify correlations between indices. Logistic regression models were used for multivariate analyses of CCI, mFI-11, and mFI-5 effectiveness in predicting patient mortality. Receiver operating characteristic (ROC) curves were generated for both unadjusted and adjusted logistic regression models. The c-statistic, also known as the area under the ROC curve (AUC), was calculated for each ROC curve. DeLong's test was used to compare the predictive ability of different models. The Hosmer-Lemeshow test using 10 groups was used to assess model goodness of fit, with a test result of $p < 0.05$ indicating lack of goodness of fit. Statistical significance was defined as $p < 0.05$.

Results

Patient Demographics

Various demographic characteristics of our 1692 patients are detailed in Table 2. The mean age ± SD of our patients was 55.5 ± 15.22 years. The majority were women (52.3%), White/Caucasian (69.9%), and married (65.5%). The mean CCI, mFI-11, and mFI-5 scores were 2.39 ± 1.86, 1.05 ± 1.19, and 0.80 ± 0.84, respectively. Meningiomas (n = 431, 25.5%) were the largest subset of primary brain tumors operated on within our cohort, followed by high-grade gliomas (n = 319, 18.9%) and pituitary tumors (n = 263, 15.5%). Nine (0.5%) patients died during their hospital admission, 15 (0.9%) died within 30 days of dis-

TABLE 2. Patient demographics (n = 1692)

Variable	Value
Mean age, yrs	55.49 ± 15.22
Sex	
Female	885 (52.3)
Male	807 (47.7)
Race	
White or Caucasian	1182 (69.9)
Black or African American	282 (16.7)
Other	228 (13.5)
Ethnicity	
Not Hispanic or Latino	1581 (93.4)
Hispanic or Latino	79 (4.7)
Patient refused to answer	13 (0.8)
Unknown	19 (1.1)
Marital status	
Married	1109 (65.5)
Single	356 (21.0)
Divorced	123 (7.3)
Widowed	90 (5.3)
Unknown	14 (0.9)
Mean score indices (median)	
CCI	2.39 ± 1.86 (2)
mFI-11	1.05 ± 1.19 (1)
mFI-5	0.80 ± 0.84 (1)
Mean KPS score	80.70 ± 16.33

Values are presented as number of patients (%) or mean ± SD unless otherwise indicated.

charge, and 29 (1.7%) died within 31–90 days of discharge. Therefore, among the patients in our cohort, there were 53 (3.1%) total cases of 90-day postoperative mortality. Table 3 displays the incidence of postoperative mortality for different types of brain tumor diagnoses found within our patient cohort. Patients with brain metastases demonstrated the highest total 90-day postoperative mortality (n = 30, 1.8%).

Bivariate Analyses of Demographics and Index Scores Upon 90-Day Postoperative Mortality

We first analyzed the number of 90-day postoperative mortality cases for each of the demographic variables that we collected for our patients in bivariate analyses. The mean age of patients who did not experience 90-day postoperative death was 55.22 years, while the mean age of patients who did experience 90-day postoperative death was 64.06 years. The mean age of patients who died postoperatively was significantly higher than that of their counterparts who did not die (p = 4.30 × 10⁻⁵). Additionally, there were 36 (4.5%) cases of 90-day postoperative mortality among 807 men compared to 17 (1.9%) cases among 885 women. In our cohort, men had a significantly higher incidence of 90-day postoperative mortality than women (OR 2.38, p = 0.0031). There was no statistically

TABLE 3. Diagnoses and postoperative mortality rates (n = 1692)

Diagnosis	Total No. of Patients	Death During 1st Admission	Death w/in 30 Days of 1st Discharge	Death w/in 31–90 Days of 1st Discharge	Total Deaths w/in 90 Days of Admission	Total Alive 90 Days After 1st Admission
Meningioma	431 (25.5)	0 (0.0)	1 (0.06)	1 (0.06)	2 (0.1)	429 (25.4)
High-grade glioma	319 (18.9)	2 (0.1)	4 (0.2)	8 (0.5)	14 (0.8)	305 (18.0)
Pituitary tumor	263 (15.5)	0 (0.0)	1 (0.06)	0 (0.0)	1 (0.06)	262 (15.5)
Brain metastasis	226 (13.4)	4 (0.2)	8 (0.5)	18 (1.1)	30 (1.8)	196 (11.6)
Other	173 (10.2)	3 (0.2)	1 (0.06)	0 (0.0)	4 (0.2)	169 (10.0)
Vestibular schwannoma	144 (8.5)	0 (0.0)	0 (0.0)	1 (0.06)	1 (0.06)	143 (8.5)
Low-grade glioma	136 (8.0)	0 (0.0)	0 (0.0)	1 (0.06)	1 (0.06)	135 (8.0)

Values are presented as number of patients (%).

significant difference in 90-day postoperative mortality as a function of patient race (p = 0.57), ethnicity (p = 0.51), or marital status (p = 0.46).

The predictive ability of each frailty index was then analyzed by bivariate analyses containing CCI, mFI-11, or mFI-5 as the sole independent variable and with 90-day patient mortality serving as the dependent variable. In these bivariate analyses, CCI (OR 4.03, p = 5.09×10^{-5}), mFI-11 (OR 4.11, p = 4.0×10^{-5}), and mFI-5 (OR 2.29, p = 0.00061) were all significant predictors of mortality. Next, we assessed 90-day postoperative mortality as a function of dichotomized CCI, mFI-11, and mFI-5 scores according to the median. The median CCI, mFI-11, and mFI-5 scores were 2, 1, and 1, respectively. There were 6 (0.9%) cases of 90-day postoperative mortality among 656 patients with a CCI of < 2 and 47 (4.5%) cases of postoperative mortality among 1036 patients with a CCI of ≥ 2. In bivariate analysis, patients with CCI ≥ 2 demonstrated significantly higher 90-day postoperative mortality relative to their counterparts (OR 5.14, p = 1.05×10^{-5}). There were 5 (0.8%) cases of 90-day postoperative mortality among 656 patients with an mFI-11 score of 0 and 48 (4.6%) cases of 90-day postoperative mortality among 1036 patients with an mFI-11 score ≥ 1. In bivariate analysis, patients with mFI-11 scores ≥ 1 demonstrated significantly higher 90-day postoperative mortality relative to their counterparts (OR 6.32, p = 2.12×10^{-6}). There were 22 (2.1%) cases of 90-day postoperative mortality among 1049 patients with an mFI-5 score of 0 and 31 (4.8%) cases of 90-day postoperative mortality among 643 patients with an mFI-5 score ≥ 1. In bivariate analysis, patients with mFI-5 scores ≥ 1 demonstrated significantly higher 90-day postoperative mortality relative to their counterparts (OR 2.36, p = 0.0024).

Multivariate Analyses of Demographics and Index Scores Upon 90-Day Postoperative Mortality

Next, adjusted logistic regression models were created using each index alongside the covariates of age, sex, race, ethnicity, marital status, and diagnosis upon 90-day postoperative mortality. For the CCI model, female sex (OR 0.51, p = 0.032) was associated with significantly decreased odds of 90-day postoperative mortality. Diagnoses of high-grade glioma (OR 0.35, p = 0.0025), vestibular schwannoma (OR 0.076, p = 0.013), meningioma (OR 0.038, p = 1.02

$\times 10^{-5}$), pituitary tumor (OR 0.029, p = 0.0064), low-grade glioma (OR 0.076, p = 0.013), or other tumor (OR 0.20, p = 0.0041) were all independently associated with a significantly decreased risk of 90-day postoperative mortality compared to a diagnosis of brain metastases. Notably, CCI score itself was not a significant predictor of 90-day mortality in multivariate analysis. When age was removed as a covariate from the logistic regression model, CCI score became a significant predictor of 90-day postoperative mortality (OR 2.52, p = 0.045). For the mFI-11 model, an mFI-11 score ≥ 1 (OR 4.19, p = 0.0043) was independently associated with increased odds of 90-day postoperative mortality, while diagnoses of high-grade glioma (OR 0.35, p = 0.0029), vestibular schwannoma (OR 0.071, p = 0.010), meningioma (OR 0.036, p = 7.12×10^{-6}), pituitary tumor (OR 0.027, p = 0.0047), low-grade glioma (OR 0.078, p = 0.014), and other tumor type (OR 0.20, p = 0.0036) were all independently associated with decreased odds of 90-day postoperative mortality compared to a diagnosis of brain metastases. For the mFI-5 model, an mFI-5 score ≥ 1 (OR 2.56, p = 0.0018) and each 1-year increase in patient age (OR 1.03, p = 0.013) were associated with increased odds of 90-day postoperative mortality, while female sex (OR 0.50, p = 0.029) and diagnoses of high-grade glioma (OR 0.33, p = 0.0014), vestibular schwannoma (OR 0.061, p = 0.0068), meningioma (OR 0.032, p = 3.65×10^{-6}), pituitary tumor (OR 0.024, p = 0.0031), low-grade glioma (OR 0.071, p = 0.010), and other tumor type (OR 0.18, p = 0.0023) relative to a diagnosis of brain metastases were all significantly associated with decreased odds of 90-day postoperative patient mortality, as shown in Table 4. The CCI, mFI-11, and mFI-5 models had p values of 0.93, 0.74, and 0.88, respectively, via the Hosmer-Lemeshow test, indicating goodness of fit for all 3 frailty index models.

Statistical Comparison Between CCI, mFI-11, and mFI-5 Scores

Correlations between the 3 indices within our patient population were calculated using Spearman's rho. The correlations between the mFI-11 and mFI-5, mFI-11 and CCI, and mFI-5 and CCI scores were 0.88, 0.55, and 0.47, respectively. All correlations were statistically significant at a level of p < 0.01. Unadjusted ROC curves were created for the CCI, mFI-11, and mFI-5 scores, with Fig. 1 depicting these curves with a reference line and

TABLE 4. Multivariate analysis of associations of frailty index types and demographic variables with total postoperative mortality

Variable	Multivariate Analysis of 90-Day Postop Mortality								
	CCI			mFI-11			mFI-5		
	OR	p Value	95% CI	OR	p Value	95% CI	OR	p Value	95% CI
Index									
CCI	1.32	0.63	0.44–4.29	—	—	—	—	—	—
mFI-11	—	—	—	4.19	0.0043*	1.70–12.66	—	—	—
mFI-5	—	—	—	—	—	—	2.56	0.0018*	1.42–4.67
Patient age, yrs	1.03	0.050	1.00–1.06	1.02	0.14	0.99–1.04	1.03	0.013*	1.01–1.06
Sex									
Male	Ref	—	—	Ref	—	—	Ref	—	—
Female	0.51	0.032*	0.27–0.93	0.55	0.062	0.29–1.02	0.50	0.029*	0.26–0.92
Race									
White or Caucasian	Ref	—	—	Ref	—	—	Ref	—	—
Black or African American	1.67	0.18	0.76–3.44	1.51	0.29	0.68–3.14	1.74	0.15	0.79–3.63
Other	1.28	0.65	0.40–3.32	1.34	0.59	0.42–3.51	1.47	0.47	0.45–3.88
Ethnicity									
Hispanic or Latino	Ref	—	—	Ref	—	—	Ref	—	—
Not Hispanic or Latino†	1.71	0.63	0.29–32.89	1.83	0.58	0.31–35.45	2.20	0.48	0.36–43.30
Marital status									
Married	Ref	—	—	Ref	—	—	Ref	—	—
Not married‡	1.31	0.39	0.70–2.40	1.27	0.44	0.68–2.34	1.37	0.32	0.73–0.52
Diagnosis									
Brain metastases	Ref	—	—	Ref	—	—	Ref	—	—
High-grade glioma	0.35	0.0025*	0.17–0.68	0.35	0.0029*	0.17–0.69	0.33	0.0014*	0.16–0.64
Vestibular schwannoma	0.076	0.013*	0.0042–0.38	0.071	0.010*	0.0039–0.34	0.061	0.0068*	0.0034–0.30
Meningioma	0.038	1.02×10^{-5}*	0.0060–0.13	0.036	7.12×10^{-6}*	0.0057–0.12	0.032	3.65×10^{-6}*	0.0051–0.11
Pituitary tumor	0.029	0.0064*	0.0016–0.14	0.027	0.00047*	0.0015–0.13	0.024	0.00031*	0.0013–0.12
Low-grade glioma	0.20	0.0041*	0.058–0.54	0.078	0.014*	0.0043–0.38	0.071	0.010*	0.0039–0.35
Other	0.076	0.013*	0.0042–0.38	0.20	0.0036*	0.057–0.53	0.18	0.0023*	0.052–0.49

* Statistically significant (p < 0.05).
† Includes patients who are not Hispanic or Latino, patients who refused to answer, and patients with an unknown ethnicity.
‡ Includes patients who are single, divorced, widowed, or have an unknown marital status.

with 90-day patient mortality serving as the dependent variable. The c-statistics (AUCs) for the unadjusted CCI, mFI-11, and mFI-5 curves were 0.67 (CI 0.63–0.70), 0.65 (CI 0.61–0.69), and 0.61 (CI 0.54–0.67), respectively. Adjusted ROC curves were then created for all 3 indices, with the following covariates included in each logistic regression model alongside the index itself: age, sex, race, ethnicity, marital status, and diagnosis. Figure 2 depicts adjusted ROC curves for CCI, mFI-11, and mFI-5. The c-statistics for the adjusted CCI, mFI-11, and mFI-5 ROC curves were 0.86 (CI 0.82–0.90), 0.87 (CI 0.83–0.91), and 0.87 (CI 0.83–0.91), respectively. Using the DeLong test to compare the AUCs for the 3 frailty indices, we found that there was no significant difference when comparing any pair of the unadjusted ROC curves. While there was a significant difference between the adjusted AUCs of the CCI and mFI-11 (p = 0.032), there was no significant difference between either of these 2 indices compared to the mFI-5 AUC.

Discussion
### Previous Research
Charlson Comorbidity Index

There have been many prior studies aimed at determining factors predictive of complications and mortality among medical and surgical patients. A 1987 study by Charlson et al. introduced the Charlson Comorbidity Index (CCI), a weighted index used to predict mortality risk from comorbid diseases in a longitudinal study.[18] The CCI has been applied within neurosurgery in an effort to risk stratify patients and better predict mortality based upon preexisting comorbidities. A 2011 study by Grossman et al. found that, among elderly patients with metastatic brain tumors, a higher CCI score (per incremental increase) was an important prognostic factor for greater hospital length of stay, higher total hospital charges, higher number of postoperative complications, and greater inpatient mortality.[12] Nuño et al. found that a patient's CCI (per incremental increase) was significantly associated with increased oc-
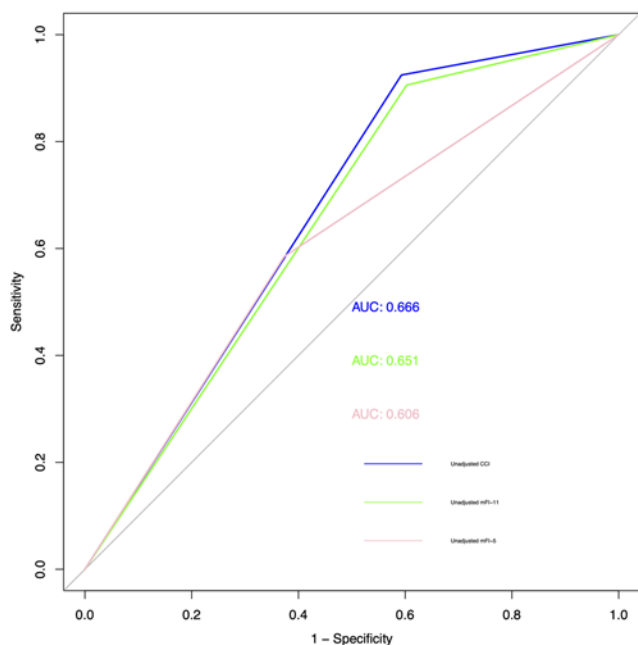
FIG. 1. Unadjusted ROC curves. The *gray diagonal line* corresponds to the reference curve. The *blue curve* corresponds to the CCI. The *green curve* corresponds to the mFI-11. The *pink curve* corresponds to the mFI-5. Figure is available in color online only.
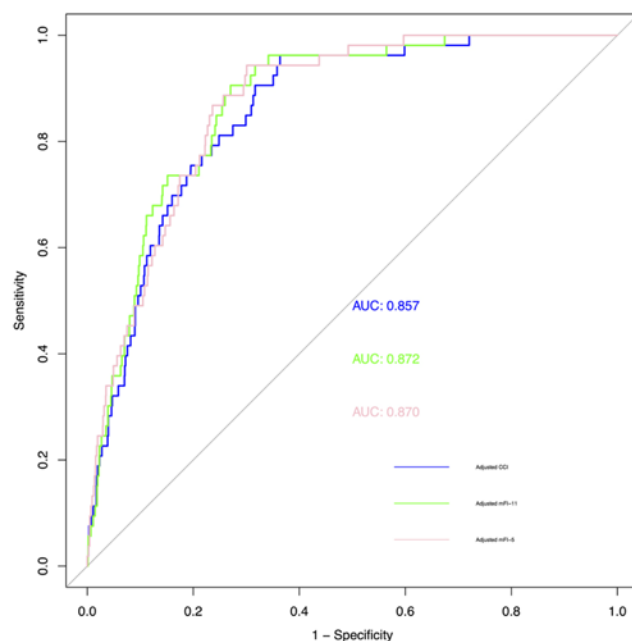
FIG. 2. ROC curves adjusted for age, sex, race, ethnicity, marital status, and diagnosis. The *gray diagonal line* corresponds to the reference curve. The *blue curve* corresponds to the CCI. The *green curve* corresponds to the mFI-11. The *pink curve* corresponds to the mFI-5. Figure is available in color online only.

currence of in-hospital mortality (p < 0.0001), patient safety indicators (metrics used to identify in-hospital patient safety events such as postoperative sepsis; p < 0.0001), and hospital-acquired conditions (undesired conditions arising during a hospital stay, such as catheter-associated urinary tract infection; p < 0.0001).[14] Ening and colleagues found that a CCI score > 3, dichotomized according to the median, was significantly associated with poor progression-free survival (p < 0.002) and overall survival (p < 0.0001) among glioblastoma patients; Ening et al. also found that patients older than 65 years demonstrated a greater proportion of comorbidities, manifesting as CCI scores > 3 (p < 0.0001).[1] Importantly, the present study utilizes a cohort of patients with a younger median age and a lower median CCI score compared to the cohort studied by Ening et al., explaining our choice of dichotomizing the CCI at a score of 2 rather than 3.

11-Factor Modified Frailty Index

As described by Subramaniam et al., the mFI-11 was developed from efforts to abbreviate a 70-item frailty index originally developed by the Canadian Study of Health and Aging that had proved difficult to apply in clinical and research settings because many of its factors were either not regularly collected or difficult to measure in patients.[6,19] A study by Imaoka et al. found that the mFI-11 was an effective predictor of postoperative outcomes among patients undergoing surgical intervention to treat spontaneous intracerebral hemorrhage (sICH), with a higher mFI-11 score (per incremental increase) being independently associated with mortality 6–8 months after sICH (p < 0.001).[5] Studying a national cohort of patients from the American Col-

lege of Surgeons National Surgical Quality Improvement Program (NSQIP) database, Youngerman and colleagues additionally established the mFI-11 as an independent predictor of 30-day adverse postoperative outcomes among brain tumor patients. Such outcomes included mortality, severe medical complications, prolonged length of stay, and unfavorable discharge.[11] Our present study further underscores the effectiveness of the mFI-11 in predicting postoperative mortality among brain tumor patients.

5-Factor Modified Frailty Index

The 5-factor modified frailty index (mFI-5) was developed from the mFI-11 after removal and changes to variables within the NSQIP database in 2012 made accurate use of the mFI-11 unfeasible. Subramaniam and colleagues compared the predictive ability of both indices for mortality, postoperative infection, and unplanned 30-day readmission in surgical patients and found that the mFI-11 and mFI-5 scores were equally effective predictors among all subspecialties that they investigated.[6] Studying the mFI-5 as a continuous variable and examining neurosurgical procedures specifically, the investigators found that an incremental increase in the mFI-5 score was significantly associated with mortality in both bivariate (OR 23.06, p < 0.0001, CI 14.38–35.97) and multivariate (OR 5.03, p < 0.0001, CI 2.95–8.58) analysis.[6] Traven et al. applied the mFI-5 to predict morbidity and mortality following primary hip and knee arthroplasty. Using logistic regression models for multivariate analyses, Traven et al. found that, for every 1-point increase in mFI-5 score, there was a significant increase in the incidence of 30-day

TABLE 5. Studies examining cranial neurosurgical patient outcomes using the CCI and the mFI-11

CCI			mFI-11		
Authors & Year	Patient Population	Findings	Authors & Year	Patient Population	Findings
Grossman et al., 2011[12]	4907 pts w/ metastatic brain tumors, mean age 72.1 yrs	Greater CCI score associated w/ increased odds of death, longer hospital LOS, & higher hospital charges	Cloney et al., 2016[25]	243 geriatric glioblastoma pts (mean age 73.1 yrs) w/ craniotomy for lobar resection	Pts w/ craniotomy for glioblastoma resection, frailty (mFI-11) w/ less aggressive intervention, longer hospital LOS, & increased complications
Grossman et al., 2011[22]	5717 pts w/ intracranial meningioma, mean age 73.6 yrs	Greater CCI score associated w/ greater odds of postop complications	Youngerman et al., 2018[11]	9149 pts underwent neurosurgical oncology procedures, 2070 (22.6%) <45 yrs, 1905 (20.8%) 45–54 yrs, 2420 (26.5%) 55–64 yrs, & 2754 (30.1%) ≥65 yrs old	Higher mFI-11 score independently associated w/ increased mortality, severe medical & neurologic complications, any complications, prolonged LOS, & unfavorable discharge
Ening et al., 2015[1]	233 pts w/ glioblastoma, median age 62 yrs	CCI score >3 significantly associated w/ poor overall & progression-free survival	Imaoka et al., 2018[5]	156 pts w/ op for intracerebral hemorrhage, mean age 66 yrs	Higher mFI-11 score significantly associated w/ unfavorable postop outcome & increased mortality
O'Neill et al., 2019[23]	123 pts w/ 131 unruptured intracranial aneurysms, mean age 70.6 yrs	CCI score independently predicted poor treatment outcome at discharge	McIntyre et al., 2019[27]	217 aSAH pts, mean age 57.6 yrs	mFI-11 score ≥2 significantly associated w/ worse aSAH grade, more complications, & increased mortality in univariate but not multivariate analysis
Schipmann et al., 2019[24]	2623 brain & spinal tumor pts w/ mean age 55.29 yrs	CCI score not correlated w/ 30-day rates of unplanned reops, unplanned readmissions, or postop mortality but significantly associated w/ surgical site infection rate	McIntyre et al., 2020[26]	75 pts w/ angiogram-negative SAH, mean age 55.4 yrs	mFI-11 score ≥1 independently predicted increased mortality & lower score predicted discharge home
—	—	—	Kim et al., 2020[21]	248 pts w/ sICH, mean age 68.5 yrs	mFI-11 score not independently associated w/ increased mortality or worse outcomes in pts w/ sICH

aSAH = aneurysmal SAH; LOS = length of stay; pt = patient; SAH = subarachnoid hemorrhage.

mortality for both primary hip (OR 1.49, p < 0.001, CI 1.28–1.73) and knee (OR 1.57, p < 0.001, CI 1.34–1.84) arthroplasty.[2] Within spine surgery, Weaver and colleagues demonstrated that higher mFI-5 scores were associated with increased postoperative complications and morbidity following elective lumbar fusions. While bivariate analysis demonstrated that stepwise increases in mFI-5 scores to 1 and ≥ 2 compared to 0 were significantly associated with 30-day mortality (p = 0.003), the significance of these results did not hold in multivariate analysis.[7] Thus, our findings are in line with the existing literature in concluding that the mFI-5 score is an effective predictor of postoperative mortality. Though there have been many studies examining cranial neurosurgical patient outcomes using both the CCI and the mFI-11 (Table 5), to our knowledge, the present study is the first to investigate the mFI-5's utility in predicting postoperative outcomes within this specific patient population.[1,5,11,12,20–27]

Results of Our Study

Given the relative ease of use of the mFI-5, our current study aimed to quantify the utility of the new mFI-5 relative to the established but more complex CCI and mFI-11 in predicting 90-day postoperative mortality among brain tumor patients. Given the significant correlation of these indices with each other via Spearman's rho (p < 0.01) as well as the fact that there was no significant difference in the predictive ability of the mFI-5 index compared with that of either the CCI or the mFI-11, our results demonstrate that the mFI-5 is similar to the CCI and mFI-11 in effectively predicting postoperative mortality in our sample of brain tumor patients. The c-statistics for our adjusted models are above 0.7, emphasizing their strong predictive value.[6] It is important to note that a likely reason why the CCI was not statistically significant in our logistic regression model (which included age as a covariate) is that the CCI weighted score is calculated using a patient's

age, and therefore it would not be expected that the index should predict 90-day postoperative mortality independently of age. Our hypothesis was confirmed when, upon removing age as a covariate in our model, CCI became an independent predictor of 90-day postoperative mortality. When age is not included as a covariate in multivariate analysis, our results regarding the CCI and postoperative mortality concur with those of Ening et al. and Nuño et al., who both found that greater CCI scores were associated with significantly poorer progression-free survival and mortality among patients with brain tumors.[1,14] Additionally, our study results obtained using the mFI-5 align with the conclusion of Youngerman et al. that the mFI-11 is an effective predictor of postoperative complications among brain tumor patients.[11]

Given the lower number of factors needed to calculate the mFI-5 and its comparable predictive value relative to mFI-11 and CCI, the mFI-5 may be a more practical choice for predicting postoperative mortality in a clinical setting where collection of fewer health variables is likely easier and more resource efficient. As discussed by Searle et al., frailty, though measured through a myriad of factors and indices, may represent a unique biological characteristic, independent of age and uniquely predictive of surgical morbidity and mortality.[10] Although the CCI, mFI-11, and mFI-5 are broadly composed of different factors, we demonstrate that they similarly predict 90-day postoperative mortality among brain tumor patients. The mFI-5 has potential to be commonly utilized in preoperative evaluations for patients with brain tumors due to its relative simplicity and predictive strength compared to more complex indices whose numerous factors may be more difficult for clinicians to obtain quickly and easily.

Study Limitations

There are various limitations to our study. Our study is retrospective and thus would benefit from validation with a study prospectively investigating the use of the CCI, mFI-11, and mFI-5 in predicting postoperative complications and mortality. The retrospective nature of the present study also prevents us from commenting on causal relationships that might exist between preoperative comorbidities and postoperative patient outcomes. Additionally, given that we only reviewed patients from a single institution, further study of the association between CCI, mFI-11, and mFI-5 with postoperative patient outcomes in a larger, multicenter cohort would serve to strengthen our conclusions. Nonetheless, given these limitations, our rigorous statistical analysis of a large cohort of 1692 brain tumor patients appears to demonstrate the utility of the mFI-5 as a predictor of 90-day postoperative mortality within this patient population.

Conclusions

In our cohort of 1692 brain tumor patients, the CCI, mFI-11, and mFI-5 are all similarly effective predictors of postoperative mortality following surgery. Considering its relative simplicity and predictive power in comparison to more complex indices requiring the collection of additional patient health variables, the mFI-5 may serve as an effective and efficient tool for the preoperative stratification of patients with primary brain tumors to identify the most ideal surgical candidates.

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Disclosures

Author Contributions

Conception and design: Khalafallah. Acquisition of data: Khalafallah, Huq. Analysis and interpretation of data: Khalafallah, Huq. Drafting the article: Khalafallah, Jimenez. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Mukherjee. Statistical analysis: Khalafallah, Huq, Jimenez. Study supervision: Brem, Mukherjee.

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