The Hospital Frailty Risk Score Independently Predicts Postoperative Outcomes in Glioblastoma Patients

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■ OBJECTIVE: **The Hospital Frailty Risk Score (HFRS) is a tool for quantifying patient frailty using International Classification of Diseases, Tenth Revision codes. This study aimed to determine the utility of the HFRS in predicting surgical outcomes after resection of glioblastoma (GBM) and compare its prognostic ability with other validated indices such as American Society of Anesthesiologists score and Charlson Comorbidity Index.**

■ METHODS: **A retrospective analysis was conducted using a GBM patient database (2017–2019) at a single institution. HFRS was calculated using International Classification of Diseases, Tenth Revision codes. Bivariate logistic regression was used to model prognostic ability of each frailty index, and model discrimination was assessed using area under the receiver operating characteristic curve. Multivariate linear and logistic regression models were used to assess for significant associations between HFRS and continuous and binary postoperative outcomes, respectively.**

■ RESULTS: **The study included 263 patients with GBM. The HFRS had a significantly greater area under the receiver operating characteristic curve compared with American Society of Anesthesiologists score ($P = 0.016$) and Charlson Comorbidity Index ($P = 0.037$) for predicting 30-day readmission. On multivariate analysis, the HFRS was significantly and independently associated with hospital length of stay ($P = 0.0038$), nonroutine discharge ($P = 0.018$), and 30-day readmission ($P = 0.0051$).**

■ CONCLUSIONS: **The HFRS has utility in predicting postoperative outcomes for patients with GBM and more effectively predicts 30-day readmission than other frailty indices. The HFRS may be used as a tool for optimizing clinical decision making to reduce adverse postoperative outcomes in patients with GBM.**

INTRODUCTION

Despite advances in surgical technique, chemotherapy, and radiation for treatment of brain tumors, the standard of care and prognosis for glioblastoma (GBM) largely has remained consistent over the past 20 years.[1,2] There is a critical need to identify and characterize preoperative risk factors for adverse postsurgical outcomes in patients with GBM.

Recently, frailty has gained prominence as a prognosticator of surgical outcomes in brain tumor patient cohorts.[3-5] In GBM, previous studies have described using patients' preoperative baseline health status, such as the American Society of Anesthesiologists (ASA) score and Charlson Comorbidity Index (CCI), in perioperative risk assessment, highlighting an association

Key words
- Frailty
- Glioblastoma
- Neuro-oncology
- Outcomes

Abbreviations and Acronyms
ASA: American Society of Anesthesiologists
AUROC: Area under the receiver operating characteristic curve
CCI: Charlson Comorbidity Index
GBM: Glioblastoma
HFRS: Hospital Frailty Risk Score
HR: Hazard ratio
ICD-10: International Classification of Diseases, Tenth Revision
mFI-5: 5-factor modified frailty index
mFI-11: 11-factor modified frailty index
LOS: Length of stay
OR: Odds ratio
OS: Overall survival
PFS: Progression-free survival

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Citation: World Neurosurg. (2024) 183:e747-e760. https://doi.org/10.1016/j.wneu.2024.01.021

*Journal homepage: **www.journals.elsevier.com/world-neurosurgery***

*Available online: **www.sciencedirect.com***

between medical comorbidities, frailty, and adverse surgical outcomes.[6,7] Other frailty indices that have demonstrated utility in predicting important patient outcomes, such as hospital length of stay (LOS), discharge disposition, hospital charges, complications, and mortality, include the 11-factor modified frailty index (mFI-11) and 5-factor modified frailty index (mFI-5).[8,9]

In an effort to create a more comprehensive and efficient measure for frailty, Gilbert et al.[10] developed the Hospital Frailty Risk Score (HFRS), a frailty index that streamlines patient frailty assessments through use of the International Classification of Diseases, Tenth Revision (ICD-10) coding system. The HFRS has been employed in orthopedic, vascular, and neurological surgery cohorts, displaying predictive ability for LOS, hospital costs, postoperative complications, and mortality.[11-14] However, applications of the HFRS to GBM patient cohorts as well as comparison with other established frailty indices have yet to be described in current literature. In the present study, we sought to understand whether the HFRS has utility in predicting surgical outcomes in GBM. We also investigated whether the HFRS demonstrates superior prognostic abilities compared with other well-established frailty indices such as ASA score, CCI, mFI-5, and mFI-11.

MATERIALS AND METHODS

Patient Selection and Recorded Variables

The present retrospective study used data from 263 patients with pathologically confirmed World Health Organization grade IV GBM who underwent surgical tumor resection or biopsy at a single institution between January 1, 2017, and December 31, 2019. Data were obtained through a combination of automated data retrieval via our institution's centralized Core for Clinical Research Data Acquisition and manual chart review. Our Institutional Review Board, acting as a Health Insurance Portability and Accountability Act Privacy Board, reviewed and approved the waiver of informed consent for this retrospective study.

ICD-10 codes were used to calculate the HFRS for each patient in our dataset, in line with the methodology of Gilbert et al.[10] **Supplementary Table 1** lists all diagnoses included in the HFRS; patients are assigned points depending on predetermined illness severity as defined by Gilbert et al. with resulting scores commonly ranging from 0 to 50. Due to our limited sample size, we elected to analyze 2 subgroups of patients based on HFRS in our bivariate analysis of postoperative outcomes: a low-frailty risk cohort with scores <5 and a medium- or high-frailty risk cohort with scores ≥ 5.[15]

The following demographic and clinical variables were collected for each patient in our study cohort: age, sex, race, HFRS, ASA score, CCI score, mFI-11 score, mFI-5 score, number of surgeries (i.e., reoperations for recurrent disease), hospital LOS, occurrence of any postoperative complications, discharge disposition, and occurrence of 30-day unplanned hospital readmission. As described in Saklad's original publication,[16] ASA scores ranged from 1 to 6 (in increments of 1), describing patients with localized disease that did not cause systemic disturbance (1) to patients with extreme systemic disorders and a poor physical state (6). The various diagnoses comprising the CCI, mFI-11, and mFI-5 are listed in **Supplementary Table 2**. The following were considered postoperative complications: deep vein thrombosis or pulmonary embolism, postoperative hematoma, new postoperative motor deficit, new postoperative language deficit, or new postoperative cognitive deficits.[17] Routine discharge disposition was defined as discharge to home with or without health care services, while nonroutine discharge was defined as discharge to a location other than home, such as a rehabilitation center or skilled nursing facility. Chart review was also conducted to determine whether patients were admitted through the emergency department and whether they completed the Stupp protocol for adjuvant chemoradiation postoperatively.[18] Relevant molecular data included *MGMT* methylation status and *IDH-1* mutation status.[19-21] Based on prior conventions, volumetric measurements were made for contrast-enhancing regions of T1-weighted preoperative imaging using Livewire Mode Segmentation in CareStream Vue PACS version 12.2.2.0105 (CareStream Health, Inc., Rochester, New York, USA).[22]

Statistical Analysis

Data were collected using Microsoft Excel version 2016 (Microsoft Corp., Redmond, Washington, USA) and analyzed using R version 4.0.2 statistical software (R Foundation for Statistical Computing, Vienna, Austria). Due to violations of the normality assumption confirmed via the Shapiro-Wilk test, the Mann-Whitney U test was used to test for significant statistical associations among continuous variables, while Fisher exact test was used to test for significant statistical associations among categorical variables. Bivariate analyses were used to model the prognostic ability of each frailty index for predicting postoperative outcomes, with model discrimination assessed using the area under the receiver operating characteristic curve (AUROC) and the DeLong test used to test for significant differences between AUROCs. To facilitate receiver operating curve analysis when comparing frailty indices, LOS was dichotomized at the 75th percentile and analyzed as binary outcome variables, in line with prior research.[23,24] Multivariate linear and logistic regression models were used to assess for significant associations between the HFRS and postoperative outcomes when controlling for other patient demographic and clinical characteristics. Bivariate and multivariate analysis of progression-free survival (PFS) and overall survival (OS) were conducted using Cox proportional hazards models, with multivariate models including as covariates all variables that attained a significance level of $P < 0.10$ in bivariate analysis.

RESULTS

Patient Demographics and Outcomes

Table 1 summarizes the demographic and clinical characteristics of our study cohort. The majority of our 263 patients were male (63.1%) and White (85.6%). The mean ± SD HFRS in patients was 5.46 ± 4.86, while the mean ASA, CCI, mFI-11, and mFI-5 scores were 2.74 ± 0.56, 3.42 ± 1.82, 1.04 ± 1.16, and 0.79 ± 0.84, respectively. There were 63 (24.0%) patients admitted through the emergency department. Regarding tumor molecular data, 86 (32.7%) patients had confirmed *MGMT* methylation, 166 (63.1%) did not have methylation, and 11 (4.2%) had unknown

Table 1. Patient Demographic and Clinical Characteristics ($N = 263$)

Characteristic	Mean þm SD or Number (%)
Age, years	58.59 ± 13.25
Sex	
Male	166 (63.1)
Female	97 (36.9)
Race	
White	225 (85.6)
Non-White	37 (14.1)
HFRS	5.46 ± 4.86
CCI	3.42 ± 1.82
mFI-11	1.04 ± 1.16
mFI-5	0.79 ± 0.84
ASA score	2.74 ± 0.56
Seizure at presentation	
Yes	88 (33.5)
No	175 (66.5)
Emergency department admission	
Yes	63 (24.0)
No	200 (76.0)
Positive *MGMT* methylation status	
Yes	86 (32.7)
No	166 (63.1)
Unknown	11 (4.2)
IDH-1 mutation	
Yes	22 (8.4)
No	241 (91.6)
Preoperative T1 postcontrast enhancing volume, cm^3	29.13 ± 27.66
Stupp protocol	
Completed	145 (55.1)
Did not complete	118 (44.9)
Number of surgeries	
1	190 (72.2)
>1	73 (27.8)
LOS, years	5.13 ± 5.50
Any postoperative complication	
Yes	49 (18.6)
No	214 (81.4)
Discharge disposition	
Nonroutine	63 (24.0)
Routine	200 (76.0)
Readmitted within 30 days	
Yes	44 (16.7)
No	219 (83.3)
Recurrence-free survival, months	6.66 ± 5.33
Overall survival, months	11.20 ± 7.50

HFRS, Hospital Frailty Risk Score; CCI, Charlson Comorbidity Index; mFI-11, 11-factor modified frailty index; mFI-5, 5-factor modified frailty index; ASA, American Society of Anesthesiologists; LOS, length of stay.

methylation status. A minority of patients (8.4%) had *IDH-1* mutation. The mean preoperative T1 postcontrast enhancing tumor volume measured in our cohort was 29.13 ± 27.66 cm^3. The Stupp protocol was completed by 55.1% of patients, and most patients in our cohort (72.2%) were undergoing their first surgery for tumor resection. The mean hospital LOS in patients was 5.13 ± 5.50 days, and 49 (18.6%) patients experienced a postoperative complication following tumor resection. Most patients (76.0%) had a routine discharge after surgery, and 44 (16.7%) patients were readmitted to the hospital within 30 days of discharge.

Bivariate HFRS Subset Analysis

Table 2 summarizes our bivariate analysis examining differences in patient demographic and clinical characteristics among our low- and medium- to high-risk frailty cohorts. There were significant positive associations between patient HFRS score and CCI ($P < 0.0001$), in addition to between HFRS and mFI-11 ($P < 0.001$). Further, patients in the medium- to high-risk HFRS frailty cohort were significantly more likely to have higher ASA scores ($P = 0.0030$). While there was a positive trend between HFRS and mFI-5, this trend did not attain statistical significance ($P = 0.056$). A significantly smaller proportion of patients (47.9% vs. 61.0% $P = 0.035$) in the medium- to high-risk frailty cohort completed the Stupp protocol postoperatively compared with the low-risk frailty cohort. Notably, there were insufficient data to determine whether there were differences in reasoning behind ending the Stupp protocol prematurely between low-frailty and medium- to high-frailty risk cohorts. Regarding postoperative outcomes, patients in the medium- to high-risk frailty cohort had significantly longer hospital LOS ($P < 0.001$), were significantly more likely to experience nonroutine discharge disposition ($P < 0.001$), and were significantly more likely to be readmitted to the hospital within 30 days of discharge ($P < 0.001$).

HFRS Comparative Analysis with Other Frailty Indices

We also conducted a comparative analysis examining the discriminative ability of the HFRS for predicting postoperative outcomes compared with the ASA score, CCI, mFI-11, and mFI-5.

Table 2. Bivariate Analysis of Hospital Frailty Risk Score and Postoperative Outcomes ($N = 263$)

Characteristic	Low Frailty Risk Cohort (HFRS <5) ($n = 146$)	Medium or High Frailty Risk Cohort (HFRS ≥5) ($n = 117$)	*P* Value
Age, years	57.72 ± 12.16	59.67 ± 14.48	0.12
Sex			
Male	95 (65.1)	71 (60.7)	0.52
Female	51 (34.9)	46 (39.3)	
Race			
White	130 (89.0)	96 (82.1)	0.11
Non-White	16 (11.0)	21 (17.9)	
CCI	2.80 ± 1.51	4.20 ± 1.88	< 0.0001*
mFI-11	0.79 ± 0.93	1.35 ± 1.33	< 0.001*
mFI-5	0.69 ± 0.77	0.92 ± 0.92	0.056
ASA score	2.66 ± 0.58	2.86 ± 0.52	0.0030*
Seizure at presentation			
Yes	45 (31.5)	43 (36.8)	0.36
No	101 (69.2)	74 (63.2)	
Emergency department admission			
Yes	34 (23.3)	29 (24.8)	0.77
No	112 (76.7)	88 (75.2)	
Positive *MGMT* methylation status			
Yes	44 (30.1)	42 (35.9)	0.35
Unknown	6 (4.1)	5 (4.3)	1.00
No	96 (65.8)	70 (59.8)	Reference†
IDH-1 mutation			
Yes	9 (6.2)	13 (11.1)	0.18
No	137 (93.8)	104 (88.9)	
Preoperative T1 postcontrast enhancing volume, cm^3	28.12 ± 27.62	30.39 ± 27.78	0.26
Stupp protocol			
Completed	89 (61.0)	56 (47.9)	0.035*
Did not complete	57 (39.0)	61 (52.1)	
Number of surgeries			
>1	40 (27.4)	33 (28.2)	
1	106 (72.6)	84 (71.8)	
LOS, days	4.15 ± 3.40	6.36 ± 7.16	< 0.001*
Any postoperative complication			
Yes	22 (15.1)	27 (23.1)	0.11
No	124 (84.9)	90 (76.9)	
Discharge disposition			
Nonroutine	23 (15.8)	40 (34.2)	< 0.001*
Routine	123 (84.2)	77 (65.8)	
Readmitted within 30 days			
Yes	13 (8.9)	31 (26.5)	< 0.001*
No	133 (91.1)	86 (73.5)	

Values are reported as mean ± SD or number (%).
HFRS, Hospital Frailty Risk Score; CCI, Charlson Comorbidity Index; mFI-11, 11-factor modified frailty index; mFI-5, 5-factor modified frailty index; ASA, American Society of Anesthesiologists; LOS, length of stay.
*Statistical significance ($P < 0.05$).
†Reference is the HFRS area under the receiver operating characteristic curve.

We found no significant differences in discrimination of the 5 indices when predicting prolonged LOS, postoperative complications, or discharge disposition. While the HFRS performed as well as the mFI-11 (0.68 vs. 0.58, P = 0.065) and mFI-5 (0.68 vs. 0.57, P = 0.066) in predicting 30-day readmission, the HFRS had a significantly higher area under the curve than both the ASA score (0.68 vs. 0.54, P = 0.016) and the CCI (0.68 vs. 0.51, P = 0.037) in predicting this outcome. Figure 1 displays the receiver operating curve curves used for comparing the discrimination of the 5 frailty indices when predicting 30-day hospital readmission.

Multivariate Analyses of Postoperative Outcomes

Table 3 summarizes the results of the multivariate analysis examining the associations between HFRS, hospital LOS, nonroutine discharge disposition, and 30-day hospital readmission. Importantly, in addition to including the HFRS, all multivariate models also included the following factors as covariates: patient age, race, preoperative seizures, emergency department admission status, *MGMT* methylation status, *IDH-1* mutation status, tumor volume, Stupp protocol completion, and repeat surgery status. Our analyses demonstrate that when controlling for these patient demographic and clinical characteristics, the HFRS remains a significant and independent predictor of hospital LOS (linear regression coefficient = 0.19, P = 0.0038), nonroutine discharge (odds ratio [OR] = 1.08, P = 0.018), and 30-day hospital readmission (OR = 1.10, P = 0.0051).

PFS and OS Analysis

Table 4 summarizes the results of our bivariate survival analysis examining predictors of both PFS and OS. Regarding PFS, patients who completed the Stupp protocol had a significantly lower risk of recurrence compared with patients who did not complete the protocol (hazard ratio [HR] = 0.58, P < 0.001), while patients who had 30-day hospital readmission were significantly more likely to experience recurrence relative to patients who were not readmitted (HR = 1.53, P = 0.031). Regarding OS,

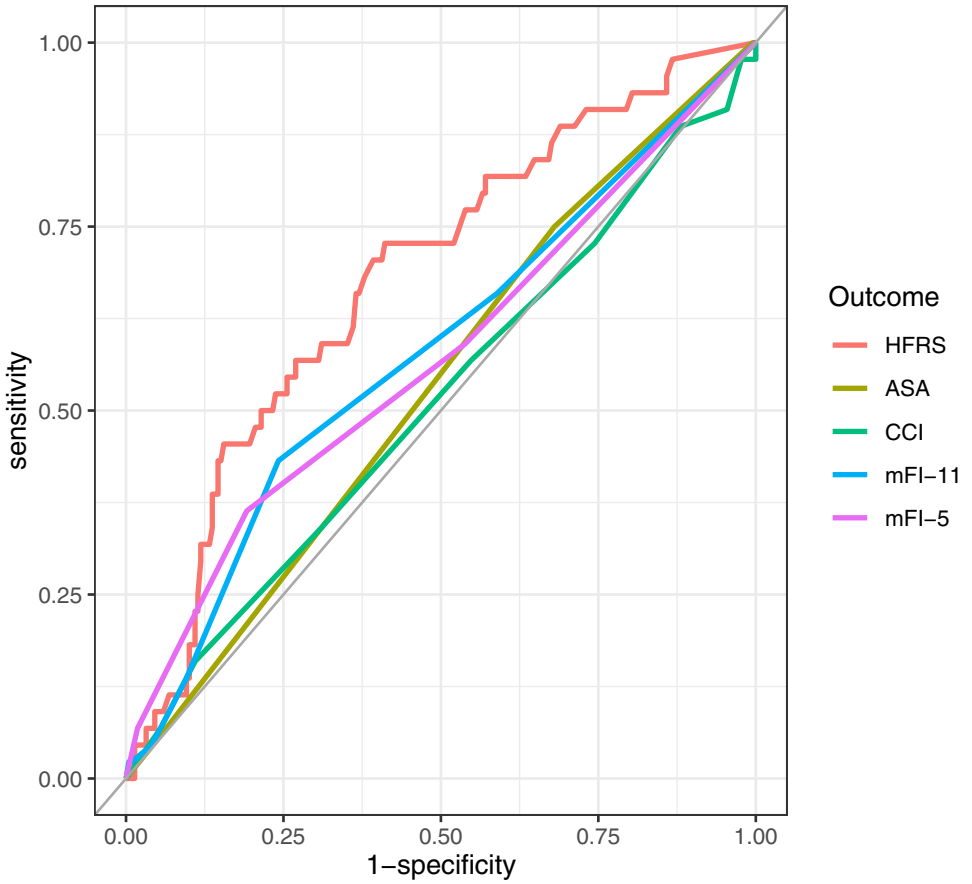

Figure 1. Receiver operating characteristic curves comparing diagnostic ability of frailty indices for predicting 30-day readmission. HFRS, Hospital Frailty Risk Score; ASA, American Society of Anesthesiologists (score); CCI, Charlson Comorbidity Index; mFI-11, 11-factor modified frailty index; mFI-5: 5-factor modified frailty index.

factors significantly associated with a lower risk of death included positive *MGMT* methylation mutation status (HR = 0.58, P < 0.0012) and Stupp protocol completion (HR = 0.51, P < 0.0001).

Table 3. Multivariate Analysis of Hospital Frailty Risk Score upon Postoperative Outcomes ($N = 263$)

Outcome	Coefficient OR	95% CI	*P* Value
Hospital LOS, days	0.19	0.061–0.31	0.0038*
Nonroutine discharge	1.08	1.01–1.15	0.018*
30-day readmission	1.10	1.03–1.18	0.0051*

All models adjusted for patient age, race, preoperative seizures, emergency department admission status, MGMT methylation status, IDH-1 mutation status, tumor volume, Stupp protocol completion, and repeat surgery status.
OR, odds ratio; CI, confidence interval; LOS, length of stay.
*Statistical significance ($P < 0.05$).

Factors that were significantly associated with a higher risk of death included older patient age (HR = 1.02, P < 0.001), higher HFRS (HR = 1.03, P = 0.024), higher CCI (HR = 1.18, P < 0.001), higher mFI-11 (HR = 1.24, P < 0.001), higher mFI-5 (HR = 1.24, P = 0.012), higher ASA score (HR = 1.45, P = 0.0055), greater tumor volume (HR = 1.01, P = 0.0090), undergoing a repeat surgery (HR = 1.73, P < 0.001), longer hospital LOS (HR = 1.04, P = 0.0016), experiencing nonroutine discharge disposition (HR = 1.64, P = 0.0034), and readmission to the hospital within 30 days of discharge (HR = 1.75, P = 0.0030).

Table 5 summarizes the multivariate survival analysis examining significant predictors of PFS and OS. Factors that were significantly and independently associated with lower risk of tumor recurrence included positive *MGMT* methylation mutation status (HR = 0.70, P = 0.026) and Stupp protocol completion (HR = 0.59, P < 0.001). Regarding OS, factors significantly and independently associated with a higher risk of death included older patient age (HR = 1.02, P = 0.025), repeat surgery (HR = 2.07, P < 0.0001), increased hospital

Table 4. Bivariate Recurrence-Free and Overall Survival Analysis ($N = 263$)

	Recurrence-Free Survival (months)			Overall Survival (months)		
Characteristic	**HR**	**95% CI**	***P* Value**	**HR**	**95% CI**	***P* Value**
Age	1.01	0.99—1.02	0.38	1.02	1.01—1.034	< 0.001*
Sex						
Male	0.91	0.67—1.23	0.53	1.09	0.81—1.46	0.59
Female						
Race						
White	0.12	0.71—1.77	0.63	0.89	0.58—1.39	0.64
Non-White						
HFRS	1.01	0.98—1.04	0.38	1.03	1.004—1.056	0.024*
CCI	1.01	0.92—1.10	0.89	1.18	1.09—1.29	< 0.001*
mFI-11	1.08	0.94—1.24	0.28	1.24	1.10—1.41	< 0.001*
mFI-5	1.12	0.95—1.33	0.18	1.24	1.05—1.46	0.012*
ASA score	0.99	0.76—1.28	0.93	1.45	1.12—1.88	0.0055*
Seizure at presentation						
Yes	1.13	0.84—1.53	0.42	0.85	0.62—1.15	0.29
No						
Emergency department admission						
Yes	1.14	0.82—1.60		1.26	0.91—1.74	0.17
No						
Positive *MGMT* methylation status						
Yes	0.73	0.53—1.00	0.051	0.58	0.42—0.81	0.0012*
Unknown	1.01	0.45—2.31	0.97	1.05	0.49—2.24	0.91
No	Reference	—	—	Reference	—	—
IDH-1 mutation						
Yes	0.79	0.46—1.35	0.39	0.71	0.41—1.23	0.22
No						
Preoperative T1 postcontrast enhancing volume, cm^3	1.00	0.99—1.01	0.89	1.01	1.00—1.01	0.0090*
Stupp protocol						
Completed	0.58	0.43—0.79	< 0.001*	0.51	0.39—0.68	< 0.0001*
Did not complete						
Number of surgeries						
>1	0.93	0.65—1.34	0.70	1.73	1.26—2.38	< 0.001*
1						
LOS	1.02	0.99—1.05	0.24	1.04	1.01—1.06	0.0016*
Any postoperative complication						
Yes	1.19	0.82—1.74	0.37	1.21	0.84—1.74	0.30
No						
Discharge disposition						

Continues

Table 4. Continued

	Recurrence-Free Survival (months)			Overall Survival (months)		
Characteristic	**HR**	**95% CI**	***P* Value**	**HR**	**95% CI**	***P* Value**
Nonroutine	1.04	0.72—1.50	0.82	1.64	1.18—2.27	0.0034*
Routine						
Readmitted within 30 days						
Yes	1.53	1.04—2.26	0.031*	1.75	1.21—2.54	0.0030*
No						

HR, hazard ratio; CI, confidence interval; HFRS, Hospital Frailty Risk Score; CCI, Charlson Comorbidity Index; mFI-11, 11-factor modified frailty index; mFI-5, 5-factor modified frailty index; ASA, American Society of Anesthesiologists; LOS, length of stay.
*Statistical significance ($P < 0.05$).

LOS (HR = 1.04, P = 0.0094), and 30-day hospital readmission (OR = 1.85, P = 0.0035). Conversely, the 2 factors that were significantly and independently associated with lower risk of death included positive *MGMT* methylation mutation status (HR = 0.54, P < 0.001) and Stupp protocol completion (HR = 0.60, P = 0.0012).

DISCUSSION

In our comparative analysis, the HFRS demonstrated a significantly better discriminative ability for predicting 30-day readmission relative to the ASA score and CCI. Additionally, when controlling for important demographic and clinical characteristics, the HFRS was significantly and independently associated with extended hospital LOS (OR = 0.19, P = 0.0038), nonroutine discharge disposition (OR = 1.08, P = 0.018) and 30-day readmission (OR = 1.10, P = 0.0051).

Prior Research

Frailty has emerged as an important prognosticator for postoperative surgical outcomes among patient cohorts undergoing surgery for resection of a brain tumor.[5,25,26] Huq et al.[3] performed a systematic review of studies analyzing frailty within brain tumor patient cohorts, finding that in all included studies frailty was associated with an important postoperative outcome. The review emphasized that frailty should play a significant role in risk stratification and decision making for neurosurgical cohorts specifically.

Building on these results from general brain tumor populations, several studies have investigated the utility of frailty indices in GBM patient cohorts. Cloney et al.[27] performed a retrospective review of 319 patients older than 65 years, finding that patients with higher frailty scores, as measured by the mFI-11, were significantly more likely to have extended hospital LOS (P = 0.0061) and significantly more likely to experience a greater number of postoperative complications (P = 0.0123). Similarly, Klingenschmid et al.[28] performed a review of 289 patients with GBM finding that the Rockwood Clinical Frailty Scale independently and significantly predicted OS among patients with GBM (P < 0.001). A recent study by Jimenez et al.[14] focused on a retrospective analysis of 2518 patients with intercranial brain tumors to compare the predictive ability of the HFRS with other validated indices. In comparative analysis, the HFRS had a greater AUROC than the ASA score, CCI, mFI-11, and mFI-5 for postoperative complications, hospital charges, 90-day readmissions, and nonroutine discharge disposition, demonstrating improved performance as a frailty-based model.[14] Notably, while the authors found important associations between the HFRS and surgical outcomes for intracranial brain tumors, they did not capture GBM-specific data. As a result, the present study includes important molecular data, such as the presence of *IDH-1* and *MGMT* mutations, and information on the administration of adjuvant therapies for patients with GBM specifically.

Previous studies suggest that frailty may be used to assist clinicians and patients in the development of short- and long-term care plans, with frailty described as an important risk stratification tool.[3,14,26,29] Indeed, patients with greater frailty may require different courses of care, such as reduced use of the Stupp protocol or surgical intervention, due to a perception of reduced physical resilience and a higher incidence of comorbidities that could complicate the treatment and increase toxicity risks.[1,5,7] The present study is the first to quantify the prognostic ability of HFRS for predicting postoperative outcomes related to GBM surgery while comparing its predictive utility with other validated frailty indices such as the ASA score, CCI, mFI-11, and mFI-5.

Present Study

In our study, AUROC comparisons found a significant improvement in predictive ability of the HFRS for 30-day readmission compared with the ASA score and CCI. Further, when controlling demographic and clinical characteristics on multivariate analysis, the HFRS was found to independently and significantly predict hospital LOS, nonroutine discharge disposition, and 30-day readmission in patients with GBM. Importantly, our study found no significant associations between HFRS and PFS or OS in multivariate analyses. This result is not entirely surprising given

Table 5. Multivariate Recurrence-Free and Overall Survival Analysis ($N = 263$)

	Recurrence-Free Survival (months)			Overall Survival (months)		
Characteristic	**HR**	**95% CI**	***P* Value**	**HR**	**95% CI**	***P* Value**
Age	—	—	—	1.02	1.00—1.03	0.025*
HFRS	—	—	—	0.99	0.96—1.03	0.69
CCI	—	—	—	1.11	0.98—1.25	0.092
mFI-11	—	—	—	1.16	0.85—1.57	0.34
mFI-5	—	—	—	0.90	0.62—1.31	0.58
ASA score	—	—	—	1.23	0.92—1.63	0.16
Positive *MGMT* methylation status						
Yes	0.70	0.51—0.96	0.026*	0.54	0.38—0.76	< 0.001*
Unknown	0.95	0.42—2.16	0.90	0.86	0.39—1.92	0.72
No	Reference	—	—	Reference	—	—
Preoperative T1 postcontrast enhancing volume, cm^3	—	—	—	1.01	1.00—1.01	0.058
Stupp protocol						
Completed	0.59	0.43—0.81	< 0.001*	0.60	0.44—0.82	0.0012*
Did not complete						
Number of surgeries						
>1	—	—	—	2.07	1.45—2.95	< 0.0001*
1						
LOS	—	—	—	1.04	1.01—1.06	0.0094*
Discharge disposition						
Nonroutine	—	—	—	1.04	0.72—1.50	0.85
Routine						
Readmitted within 30 days						
Yes	1.41	0.95—2.09	0.090	1.85	1.23—2.81	0.0035*
No						

HR, hazard ratio; CI, confidence interval; HFRS, Hospital Frailty Risk Score; CCI, Charlson Comorbidity Index; mFI-11, 11-factor modified frailty index; mFI-5, 5-factor modified frailty index; ASA, American Society of Anesthesiologists; LOS, length of stay.
*Statistical significance ($P < 0.05$).

that the HFRS was designed specifically for integration into acute hospital settings with the goal of predicting short-term outcomes related to medical utilization.[10] With further research validating the use of the HFRS in neurosurgical clinical workflows, the HFRS may be used as an important risk stratification tool in GBM patient cohorts.

Differences in the predictive performance of the HFRS when compared with the ASA score, CCI, mFI-11, and mFI-5 are likely driven by the different scoring methodologies used to obtain each metric. While the mFI-11 and mFI-5 consist of scales including 11 and 5 comorbidities, respectively, the HFRS consists of 109 items with varying weights.[10,30] As an example, Meyer et al.[31] recently performed a comparative analysis of frailty indices in hip and knee replacements, finding that the HFRS had improved performance in the prediction of adverse surgical outcomes compared with the mFI-5. Additionally, while the CCI weighs each of its component items, similar to the HFRS, only 17 comorbidities are taken into account in generating the CCI, potentially reducing the scope of patients to whom the tool may be applicable.[32] As ICD-10 codes are routinely collected during the course of treatment for patients with GBM, use of the 109-item HFRS may be relatively easily integrated into normative neurosurgical workflows.[14,31]

Our study found that in patients with GBM, the HFRS may have utility in predicting hospital LOS, nonroutine discharge disposition, and 30-day readmission. Notably, the association between frailty and extended hospital LOS has been well established in previous literature describing the HFRS. Previous studies suggest

that due to a diminished baseline health status relative to patients who are less frail, patients with a high HFRS may experience a greater number of postoperative complications requiring more intensive rehabilitation and an extended stay in critical care settings.[13,31,33,34] Koo et al. performed a retrospective analysis of 33,840 patients who underwent endovascular treatment for ruptured intracranial aneurysm, finding that both intermediate and high HFRS groups had increased risk of extended hospital LOS (intermediate: OR = 2.38, $P < 0.001$; high: OR = 4.49, $P < 0.001$).[34] Similarly, Elsamadicy et al. retrospectively reviewed 29,305 patients undergoing anterior cervical discectomy and fusion for cervical spondolytic myelopathy and found that moderate to high HFRS predicted extended hospital LOS (OR = 3.19, $P < 0.001$).[13]

The association we describe between the HFRS and nonroutine discharge disposition is consistent with previous studies analyzing frailty in neurosurgical cohorts. Hannah et al.[12] analyzed the performance of the HFRS in predicting surgical outcomes for degenerative spine surgery cohorts, finding that patients with a high HFRS had higher risk of nonroutine discharge (OR = 16.7, $P < 0.0001$). Similarly, Koo et al.[34] (intermediate: OR = 2.13, $P < 0.001$; high: OR = 4.17, $P < 0.001$) and Jimenez et al.[14] (OR = 1.14, $P < 0.0001$) found that the HFRS independently and significantly predicted nonroutine discharge among patients undergoing surgery for intracranial aneurysms and nonspecific brain tumors, respectively.

Our last major finding in the present study was that the HFRS was significantly and independently associated with higher rates of 30-day readmissions among patients with GBM. This finding suggests that frail patients with GBM are less likely to have uncomplicated recoveries and may experience severe enough deterioration in the weeks after surgery to require emergent medical attention. This finding is supported by Elsamadicy et al.,[35] who, analyzing 4346 patients with metastatic spinal column tumors, found that intermediate HFRS was associated with unplanned 30-day readmissions (OR = 1.32, $P = 0.012$). Similarly, Voora et al.[36] performed a retrospective analysis of 14,420 patients undergoing surgical intervention for head and neck cancer, finding that an HFRS of ≥ 5 was a significant predictor of 30-day readmission (OR = 1.59, $P < 0.001$).

Overall, our results indicate that the HFRS may serve as an effective risk stratification tool for postoperative outcomes in patients undergoing GBM surgery. Importantly, the HFRS can easily be integrated into electronic medical record systems and existing clinical workflows because it is based solely upon ICD-10 codes.

Study Limitations

Our study has several limitations that should be addressed in future research. Our study was retrospective, and as a result we were unable to determine whether the relationships between any of the variables and outcomes in our patient cohort were causal. Additionally, our results are representative only of patients treated at a single institution within the predefined time period; future studies may be performed prospectively and in larger, more heterogeneous cohorts to validate our findings and establish differences between cohorts with medium versus high frailty risk. Prospective HFRS validation studies in GBM cohorts may also look to elucidate a possible causal relationship between increased patient scores and premature completion of the Stupp protocol. Notably, our results may not be generalizable for patients with GBM who are receiving only nonsurgical treatment for their tumors. Regarding the frailty measures used in the study, we were unable to include several validated frailty indices, such as the Karnofsky Performance Scale and Risk Analysis Index, due to insufficient data. Further, given that the HFRS is derived from existing ICD-10 codes, errors in coding may have influenced our results. However, despite these limitations, our study proposes an easily implemented method for risk stratification in a specific brain tumor patient cohort and is the first comparative analysis on the efficacy of the HFRS in predicting postoperative surgical outcomes in patients with GBM.

CONCLUSIONS

The present study sought to determine the efficacy of using patient frailty, quantified through the HFRS, in predicting postoperative outcomes in patients with GBM. Compared with established frailty indices such as the ASA score, CCI, mFI-11, and mFI-5, the HFRS has significantly higher AUROC values for predicting 30-day readmission. In multivariate analysis, the HFRS independently and significantly predicted extended hospital LOS, nonroutine discharge disposition, and 30-day readmission. Overall, these findings indicate that the HFRS may be an effective tool for predicting surgical outcomes in patients with GBM.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Adrian E. Jimenez: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Writing — original draft, Writing — review & editing. **Sachiv Chakravarti:** Data curation, Investigation, Methodology, Writing — original draft, Writing — review & editing. **Jiaqi Liu:** Writing — original draft, Writing — review & editing. **Foad Kazemi:** Writing — original draft, Writing — review & editing. **Christopher Jackson:** Writing — review & editing. **Gary Gallia:** Writing — review & editing. **Chetan Bettegowda:** Writing — review & editing. **Jon Weingart:** Writing — review & editing. **Henry Brem:** Writing — review & editing. **Debraj Mukherjee:** Supervision, Writing — review & editing.

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Conflict of interest statement: Chetan Bettegowda is a consultant for Depuy Synthes, Bionaut Labs, Galectin Therapeutics, and Privo Technologies and co-founder of OrisDx and Belay Diagnostics.

Received 28 July 2023; accepted 4 January 2024

Citation: World Neurosurg. (2024) 183:e747-e760. https://doi.org/10.1016/j.wneu.2024.01.021

*Journal homepage: **www.journals.elsevier.com/world-neurosurgery***

*Available online: **www.sciencedirect.com***

SUPPLEMENTARY DATA

Supplementary Table 1. Components of the Hospital Frailty Risk Score ($N = 263$) by Weight

HFRS Component	ICD-10 Code	Weight	Number of Patients (%)
Dementia in Alzheimer disease	F00	7.1	0 (0.0)
Hemiplegia	G81	4.4	26 (9.9)
Alzheimer disease	G30	4.0	0 (0.0)
Sequelae of cerebrovascular disease	I69	3.7	1 (0.4)
Other symptoms and signs involving the nervous and musculoskeletal systems	R29	3.6	20 (7.6)
Delirium, not induced by alcohol and other psychoactive substances	F05	3.2	3 (1.1)
Other disorders of urinary system	N39	3.2	9 (3.4)
Superficial injury of head	S00	3.2	0 (0.0)
Unspecified fall	W19	3.2	8 (3.0)
Unspecified hematuria	R31	3.0	0 (0.0)
Other bacterial agents as the cause of diseases classified to other chapters	B96	2.9	1 (0.4)
Other symptoms and signs involving cognitive functions and awareness	R41	2.7	43 (16.3)
Abnormalities of gait and mobility	R26	2.6	12 (4.6)
Convulsions, not elsewhere classified	R56	2.6	94 (35.7)
Other cerebrovascular diseases	I67	2.6	4 (1.5)
Somnolence, stupor, and coma	R40	2.5	8 (3.0)
Complications of genitourinary prosthetic devices, implants, and grafts	T83	2.4	0 (0.0)
Intracranial injury	S06	2.4	6 (2.3)
Fracture of shoulder and upper arm	S42	2.3	1 (0.4)
Other disorders of fluid, electrolyte, and acid-base balance	E87	2.3	32 (12.2)
Other joint disorders, not elsewhere classified	M25	2.3	9 (3.4)
Volume depletion	E86	2.3	13 (4.9)
Senility	R54	2.2	0 (0.0)
Care involving use of rehabilitation procedures	Z50	2.1	0 (0.0)
Other fall on same level	W18	2.1	0 (0.0)
Unspecified dementia	F03	2.1	0 (0.0)
Cellulitis	L03	2.0	12 (4.6)
Problems related to medical facilities and other health care	Z75	2.0	0 (0.0)
Superficial injury of lower leg	S80	2.0	0 (0.0)
Vascular dementia	F01	2.0	0 (0.0)
Blindness and low vision	H54	1.9	13 (0.0)
Deficiency of other B group vitamins	E53	1.9	1 (0.4)
Acute renal failure	N17	1.8	57 (21.7)
Fracture of rib(s), sternum, and thoracic spine	S22	1.8	1 (0.4)
Other functional intestinal disorders	K59	1.8	13 (4.9)
Problems related to social environment	Z60	1.8	0 (0.0)
Parkinson disease	G20	1.8	4 (1.5)

ICD-10, International Classification of Diseases, Tenth Revision

Continues

Supplementary Table 1. Continued

HFRS Component	ICD-10 Code	Weight	Number of Patients (%)
Syncope and collapse	R55	1.8	8 (3.0)
Carrier of infectious disease	Z22	1.7	0 (0.0)
Decubitus ulcer	L89	1.7	1 (0.4)
Streptococcus and staphylococcus as the cause of diseases classified to other chapters	B95	1.7	1 (0.4)
Duodenal ulcer	K26	1.6	0 (0.0)
Hypotension	I95	1.6	12 (4.6)
Other septicemia	A41	1.6	10 (3.8)
Other symptoms and signs involving general sensations and perceptions	R44	1.6	0 (0.0)
Ulcer of lower limb, not elsewhere classified	L97	1.6	3 (1.1)
Unspecified renal failure	N19	1.6	18 (6.8)
Epilepsy	G40	1.5	29 (11.0)
Exposure to unspecified factor	X59	1.5	0 (0.0)
Other arthrosis	M19	1.5	26 (9.9)
Personal history of other diseases and conditions	Z87	1.5	89 (33.8)
Respiratory failure, not elsewhere classified	J96	1.5	8 (3.0)
Abnormal results of function studies	R94	1.4	4 (1.5)
Chronic renal failure	N18	1.4	69 (26.2)
Fracture of femur	S72	1.4	0 (0.0)
Fracture of lumbar spine and pelvis	S32	1.4	0 (0.0)
Osteoporosis without pathological fracture	M81	1.4	1 (0.4)
Other disorders of pancreatic internal secretion	E16	1.4	1 (0.4)
Other disorders of kidney and ureter, not elsewhere classified	N28	1.3	11 (4.2)
Retention of urine	R33	1.3	6 (2.3)
Unknown and unspecified causes of morbidity	R69	1.3	0 (0.0)
Nosocomial condition	Y95	1.2	0 (0.0)
Other and unspecified injuries of head	S09	1.2	0 (0.0)
Other degenerative diseases of nervous system, not elsewhere classified	G31	1.2	9 (3.4)
Symptoms and signs involving emotional state	R45	1.2	6 (2.3)
Transient cerebral ischemic attacks and related syndromes	G45	1.2	1 (0.4)
Unspecified urinary incontinence	R32	1.2	1 (0.4)
Diarrhea and gastroenteritis of presumed infectious origin	A09	1.1	0 (0.0)
Fall involving bed	W06	1.1	0 (0.0)
Open wound of head	S01	1.1	3 (1.1)
Other bacterial intestinal infections	A04	1.1	1 (0.4)
Other soft tissue disorders, not elsewhere classified	M79	1.1	7 (2.7)
Pneumonia, organism unspecified	J18	1.1	9 (3.4)
Problems related to care-provider dependency	Z74	1.1	21 (8.0)
Artificial opening status	Z93	1.0	1 (0.4)
Gangrene, not elsewhere classified	R02	1.0	0 (0.0)
Pneumonitis due to solids and liquids	J69	1.0	0 (0.0)

Continues

Supplementary Table 1. Continued

HFRS Component	ICD-10 Code	Weight	Number of Patients (%)
Speech disturbances, not elsewhere classified	R47	1.0	39 (14.8)
Vitamin D deficiency	E55	1.0	5 (1.9)
Fall on and from stairs and steps	W10	0.9	0 (0.0)
Fall on same level from slipping, tripping, and stumbling	W01	0.9	0 (0.0)
Other hearing loss	H91	0.9	15 (5.7)
Scoliosis	M41	0.9	3 (1.1)
Symptoms and signs concerning food and fluid intake	R63	0.9	5 (1.9)
Thyrotoxicosis (hyperthyroidism)	E05	0.9	3 (1.1)
Agent resistant to penicillin and related antibiotics	U80	0.8	0 (0.0)
Cerebral infarction	I63	0.8	15 (5.7)
Dependence on enabling machines and devices	Z99	0.8	10 (3.8)
Dysphagia	R13	0.8	12 (4.6)
Osteoporosis with pathological fracture	M80	0.8	0 (0.0)
Other diseases of digestive system	K92	0.8	3 (1.1)
Abnormalities of heart beat	R00	0.7	28 (10.6)
Calculus of kidney and ureter	N20	0.7	13 (4.9)
Mental and behavioral disorders due to use of alcohol	F10	0.7	0 (0.0)
Other medical procedures as the cause of abnormal reaction of the patient	Y84	0.7	6 (2.3)
Unspecified acute lower respiratory infection	J22	0.7	0 (0.0)
Other abnormal findings of blood chemistry	R79	0.6	10 (3.8)
Problems related to life-management difficulty	Z73	0.6	0 (0.0)
Depressive episode	F32	0.5	32 (12.2)
Open wound of forearm	S51	0.5	0 (0.0)
Personal history of risk factors, not elsewhere classified	Z91	0.5	28 (10.6)
Spinal stenosis	M48	0.5	2 (0.8)
Disorders of mineral metabolism	E83	0.4	19 (7.2)
Other anemias	D64	0.4	14 (5.3)
Other local infections of skin and subcutaneous tissue	L08	0.4	1 (0.4)
Polyarthrosis	M15	0.4	0 (0.0)
Nausea and vomiting	R11	0.3	22 (8.4)
Other noninfective gastroenteritis and colitis	K52	0.3	5 (1.9)
Fever of unknown origin	R50	0.1	11 (4.2)

ICD-10, International Classification of Diseases, Tenth Revision

Supplementary Table 2. Components of Charlson Comorbidity Index (with Associated Item Weights), 11-Factor Modified Frailty Index, and 5-Factor Modified Frailty Index

CCI (Weight)	mFI-11	mFI-5
AIDS (6)	Functional status (i.e., requiring assistance with activities of daily living)	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/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 infarct (1)		
Age (+1 each decade $\geq$ 50)		

CCI, Charlson Comorbidity Index; mFI-11, 11-factor modified frailty index; mFI-5, 5-factor modified frailty index; AIDS, acquired immunodeficiency syndrome; COPD, chronic obstructive pulmonary disease.