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Risk Analysis Index and 30-Day Mortality after Brain Tumor Resection: A Multicenter Frailty Analysis of 31,776 Patients from 2012 to 2020

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Abstract

Introduction The aim of this study was to evaluate the discriminative accuracy of the preoperative Risk Analysis Index (RAI) frailty score for prediction of mortality or transition to hospice within 30 days of brain tumor resection (BTR) in a large multicenter, international, prospective database.

Methods Records of BTR patients were extracted from the American College of Surgeons National Surgical Quality Improvement Program (2012–2020) database. The relationship between the RAI frailty scale and the primary end point (mortality or discharge to hospice within 30 days of surgery) was assessed using linear-by-linear proportional trend tests, logistic regression, and receiver operating characteristic (ROC) curve analysis (area under the curve as C-statistic).

Results Patients with BTR ($N = 31,776$) were stratified by RAI frailty tier: 16,800 robust (52.8%), 7,646 normal (24.1%), 6,593 frail (20.7%), and 737 severely frail (2.3%). The mortality/hospice rate was 2.5% ($n = 803$) and was positively associated with increasing RAI tier: robust (0.9%), normal (3.3%), frail (4.6%), and severely frail (14.2%) ($p < 0.001$). Isolated RAI was a robust discriminatory of primary end point in ROC curve analysis in the overall BTR cohort (C-statistic: 0.74; 95% confidence interval [CI]: 0.72–0.76) as well as the malignant (C-statistic: 0.74; 95% CI: 0. 67–0.80) and benign (C-statistic: 0.71; 95% CI: 0.70–0.73) tumor subsets (all $p < 0.001$). RAI score had statistically significantly better performance compared with the 5-factor modified frailty index and chronological age (both $p < 0.0001$).

Conclusions RAI frailty score predicts 30-day mortality after BTR and may be translated to the bedside with a user-friendly calculator (https://nsgyfrailtyoutcome-slab.shinyapps.io/braintumormortalityRAIcalc/). The findings hope to augment the informed consent and surgical decision-making process in this patient population and provide an example for future study designs.

Keywords
- frailty
- Risk Analysis Index
- brain Tumor
- neuro-oncology
- National Surgical Quality Improvement Program

Introduction

Background/Rationale

The rapidly aging worldwide population has increased the volume and complexity of brain tumor surgical management.[1] In the era of heightened scrutiny of postoperative complications and quality outcomes, it is essential to accurately measure preoperative risk. However, the informed consent and surgical decision-making process is often hindered by the paucity of clinical risk tools directly linked to outcomes

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relevant to specific brain tumor populations. Recent literature trends have witnessed the popularization of "frailty," a measure of baseline physiological reserve, for surgical outcomes prediction. However, there is marked heterogeneity of frailty definitions and outcome metrics, which limits the clinical generalizability.[2] To address these concerns, the authors propose a standardized frailty research initiative involving application of a standardized, validated, and easy-to-use frailty index with a manageable number of input factors.

Objectives

The Risk Analysis Index (RAI) is a robust frailty index developed and validated in surgical populations.[3,4] The RAI is uniquely versatile for both clinical prospective application with a patient-centered questionnaire and large retrospective database analysis. However, the generalizability of RAI to 30-day mortality outcomes after brain tumor resection (BTR) is presently unknown. The objective of the present study was to evaluate the discriminatory accuracy of the RAI score for prediction of mortality or discharge to hospice within 30 days of BTR in a large multicenter, prospective cohort of 31,776 patients.

Methods

Study Design

The American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database is a prospective, peer-controlled, validated database for quantifying 30-day surgical outcomes. The ACS-NSQIP is a large multicenter, international, clinical database of surgical operations representing over 700 hospitals from 49 U.S. states and 11 different countries. Data are entered from each institution prospectively by ACS-trained surgical clinical reviewers to improve consistency and reliability. This study was performed under an ACS-NSQIP Participant Use File and was considered exempt by our institutional review board.

Participants and Setting

The postoperative diagnosis fields in NSQIP (2012–2020) were queried using International Classification for Disease (ICD), 9th and 10th Revisions, Clinical Modification codes indicating resection of intracranial tumors, yielding 48,664 records. Next, the primary Current Procedural Terminology (CPT) field was searched for codes indicating craniotomy/craniectomy for BTR, yielding 47,025 records. Records with missing information for age or discharge disposition were excluded ($n = 76$). Records with operative time less than 2 hours were excluded to minimize incidental inclusion of brain biopsies and/or other procedures not related to tumor resection ($n = 11,371$).

Variables

The Revised RAI score was computed using methodology previously described in detail by Hall et al during the initial derivation/validation and subsequent recalibration.[3,4] The RAI score components include standard NSQIP variables age, sex, disseminated cancer ("DISCANC"), weight loss ("WTLOSS"), renal failure ("RENAFAIL; DIALYSIS"), congestive heart failure ("HXCHF"), shortness of breath ("DYSPNEA"), functional status ("FNSTATUS2"), and living status ("TRANST" = nursing home or chronic care facility). The RAI score was considered as a continuous variable and categorical variable stratified into tiers: *robust* (0–20), *normal* (21–30), *frail* (31–40), or *severely frail* (41+). The primary outcome, postoperative mortality, was defined as death within 30 days of operation or discharge to hospice.

Statistical Methods

The R Project for Statistical Computing version 4.2.1 (The R Foundation, Vienna, Austria) software (https://www.R-project.org/) and the SPSS Statistics version 28.0.1.1 (IBM Corporation, Armonk, New York, United States) statistical software package were utilized for analyses with a statistical significance threshold set a priori to an alpha of 0.05. Linear-by-linear proportional trends (frailty and mortality) were evaluated with the Cochran–Armitage trend test. Binary logistic regression quantified the relationship between RAI and primary end point. Discriminatory accuracy was assessed by computation of C-statistics (with 95% confidence intervals [CIs]) and interpreted using established epidemiological criteria per Hosmer–Lemeshow: outstanding (0.9–1.0), excellent (0.8–0.89), acceptable (0.7–0.79), poor (0.6–0.69), and no discrimination (0.5–0.59).[5] The DeLong test assessed whether the area under the curve for RAI was statistically significantly different from that for chronological age and the 5-factor modified frailty index (mFI-5) score. The R[6] packages rms[7] and shiny[8] were used to generate an interactive Risk Analysis Index and Brain Tumor Resection Outcomes calculator found at the following website: https://nsgyfrailtyoutcomeslab.shinyapps.io/braintumormortalityRAIcalc/.

Results

Participants

The final cohort included 31,776 patients who underwent BTR, with 22.6% benign ($n = 7,194$), 70.7% malignant ($n = 22,476$), and 6.6% with unknown pathology ($n = 2,106$).

Descriptive Data

Median (interquartile) age was 57 (45–66) years, 49% were female ($n = 15,584$), and the mean (standard deviation [SD]) RAI score was 21 (10). The mean (SD) length of stay in days was 6.8 (7.1). The mean (SD) operative time in hours was 4.2 (2.1). There were 322 in-hospital deaths (1%), 720 deaths within 30-days of operation (2.3%), and 83 discharges to hospice (0.3%). The average duration in days from operation to death was 16.3 (8.2). For subsequent analyses, postoperative "mortality" was inclusive of discharge to hospice and death within 30 days of surgery.

Outcome Data

A significant proportional trend was noted for RAI frailty category and mortality incidence after BTR: robust (0.9%), normal (3.3%), frail (4.6%), and severely frail (14.2%) ($p < 0.001$; ►**Fig. 1A**). Subgroup analysis demonstrated similar uptrends in mortality with increasing RAI frailty for

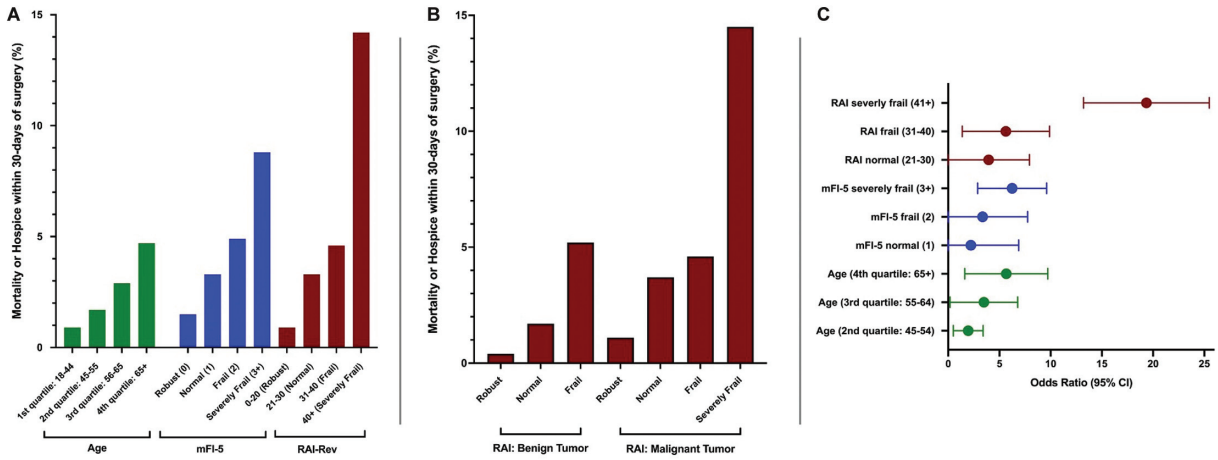

Fig. 1 (**A**) Incidence rate of hospice/mortality within 30 days of intracranial tumor resection stratified by age group and baseline frailty (measured by mFI-5 and RAI), ACS-NSQIP 2012–2020, $N = 31,776$. (**B**) Mortality rate stratified by RAI frailty in benign vs malignant tumors. (**C**) Effect sizes for primary outcome of hospice/mortality in regression analysis. Reference groups were RAI robust (score of 0–20), mFI-5 robust (score of 0), and age 1st quartile (18–44).

malignant (1.1, 3.7, 4.6, and 14.5%) and benign (0.4, 1.7%, and 5.2%) brain tumors (both $p < 0.001$; ►**Fig. 1B**).

On logistic regression, compared with robust patients, mortality/hospice was approximately 6 (odds ratio [OR]: 5.6; 95% CI: 4.6–6.9) and approximately 19 (OR: 19.4; 95% CI: 14.9–25.2) times more likely in frail and severely frail patients, respectively (both $p < 0.001$; ►**Fig. 1C**).

Main Results

Isolated RAI was a robust predictor of mortality in receiver operating characteristic (ROC) curve analysis (C-statistic: 0.74; 95% CI: 0.72–0.76; ►**Fig. 2**) in the overall BTR cohort, as well as the malignant (C-statistic: 0.74; 95% CI: 0. 67–0.80) and benign (C-statistic: 0.71; 95% CI: 0.70–0.73) subsets (all $p < 0.0001$). At RAI score thresholds of 10, 15, and 20, the sensitivity of the model for mortality was 97, 92, and 85%, respectively. At RAI score thresholds of 30, 35, and 40, the specificity of the model for mortality was 77.5, 90, and 99.9%, respectively. In terms of mortality prediction, RAI score had statistically significantly better discriminatory performance compared to mFI-5 and chronological age (both $p < 0.0001$), which were considered "poor discrimination."

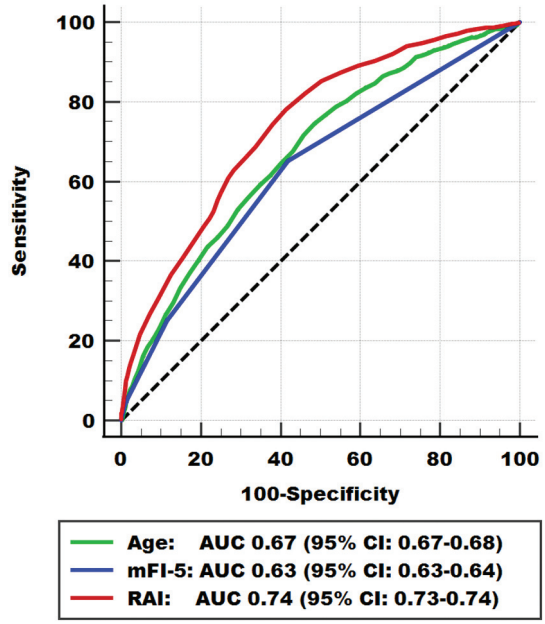

Fig. 2 Receiver operating characteristic (ROC) curve analysis demonstrating superior discriminatory accuracy of Risk Analysis Index for primary outcome of mortality or hospice transition within 30 days of intracranial tumor resection, ACS-NSQIP 2012–2020, $N = 31,776$.

Discussion

Key Results

This is the first report describing the relationship between RAI frailty score and 30-day mortality outcomes in patients undergoing craniotomy for BTR. The RAI predicts mortality after BTR with excellent discriminatory accuracy and may be translated to the bedside with a user-friendly calculator (https://nsgyfrailtyoutcomeslab.shinyapps.io/braintumor-mortalityRAIcalc/). This mortality prediction occurred even with the limited 30-day window of NSQIP outcomes, which is noteworthy, as the RAI was originally calibrated for longer-term mortality prediction.[4] We propose the RAI frailty screening cutoff score of "40" in BTR patients, which would capture 99.9% of frailty-driven mortalities and which would inform patients of the significantly elevated risk associated with BTR if they have this score. An online calculator was designed for bedside calculation of RAI with brain tumor–calibrated probability of postoperative (30-day) mortality. The present study provides critical information for preoperative risk assessment and patient/family counseling that has not been available previously.

Interpretation/Generalizability

A prior study by Thommen et al first identified an association between RAI score and in-hospital discharge outcomes after craniotomy for BTR.[9] While the study identified a correlation between frailty and discharge outcomes, it did not analyze

30-day mortality or assess comparative discriminatory accuracy. Prior studies identifying association between frailty (measured by other scales) and increased postoperative mortality after BTR include one retrospective analysis of the prospective ACS-NSQIP,[10] two analyses of billing databases,[11] and one single-center retrospective cohort study.[12] A lack of association with mortality was reported in two nationwide billing database analyses using the Johns Hopkins Adjusted Clinical Groups frailty-defining index (JHACG) [13,14] The studies found that JHACG was associated with length of stay, in-hospital complications, and nonroutine disposition, but not mortality.[9,10] Several studies have correlated mFI-5 with postoperative mortality after craniotomy for brain tumor in the NSQIP (2012–2018, $N = 20{,}333$),[10] the National Inpatient Sample (2015–2018, $N = 13{,}650$),[11] and a single-center retrospective study (January 2017 to December 2018, $N = 1{,}692$).[12–14] Comparative ROC curve analysis demonstrated statistically significant superiority of RAI versus chronological age and mFI-5. This is unsurprising, as mFI-5 does not represent the classical frailty phenotype of limited mobility, cognitive decline, impaired activities of daily living, and limited physiological reserve. The mFI-5 (and its 11-factor counterpart) are primarily tabulated numbers of comorbidities, which do not necessarily correlate with frailty.[15]

Limitations

The study accessed the relationship between RAI and postoperative outcomes and does not comment on other details relevant to neuro-oncology: tumor size, extent of resection, surgical approach, histopathological diagnosis, and adjunctive treatments. Mortality outcomes were limited to 30 days. Diagnosis and procedures within NSQIP were queried via ICD codes and CPT codes, which have inherent limitations in accuracy and granularity. However, discrepancies were mitigated by crosscheck with NSQIP descriptive fields. Despite the limitations, the excellent quality assurance measures taken by ACS-NSQIP mitigate common concerns with other nationwide databases while providing the large sample size necessary for the present analysis.[16]

Conclusion

Preoperative frailty, measured by RAI, reliably predicts 30-day mortality after BTR and had superior discriminatory accuracy compared to mFI-5. The RAI may be translated to the bedside with a user-friendly calculator. The findings hope to augment the informed consent and surgical decision-making process in this patient population and provide an example for future study designs. Prospective institution-level validation of RAI score is currently ongoing as part of a standardized frailty research initiative at our institution.

Conflict of Interest
None declared.

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