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Original Article

Frailty is associated with mortality in brain tumor patients

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Abstract: Frailty represents a state of vulnerability that increases the risk of adverse health outcomes. In the last years, frailty has emerged as a good indicator of patient's functional reserve and it seems to be a predictor of negative outcomes in oncological patients. In this work, we analyzed the clinical utility of frailty as preoperative risk assessment tool in a brain tumor cohort from Donostia University Hospital (Spain). For that, we used several frailty tools consisting of questionnaires based on frailty phenotype (FRAIL scale), evaluating functional performance (Gait Speed) and a self-report questionnaire that includes variables related to the physical, cognitive and psychosocial domains of frailty (Tilburg Frailty Indicator). We identified a higher percentage of patients in vulnerable situation prior to surgery when using frailty tools compared to routine scales such as Karnosfky score and Barthel Index. Remarkably, patients diagnosed with malignant tumors were frailer and presented significant less six-month survival than patients with benign tumors by all the frailty scales abovementioned. In line with this, the vast majority of patients that became pre-frail or frail after neurosurgery (by FRAIL scale) harbored a malignant tumor. Moreover, frailty status significantly correlated with patient's mortality and autonomy, but not with the presence of postoperative outcomes in our cohort. Taken together, our results show that frailty measurement, mainly by FRAIL scale, is a useful tool to evaluate preoperative risk in brain tumor patients as well as patient's prognosis after neurosurgery.

Keywords: Frailty, brain tumor, neurosurgery, postoperative outcome, mortality, FRAIL scale

Introduction

Frailty represents a state of vulnerability that leads to an impaired capacity to respond against stressors, thereby increasing the risk of adverse health outcomes [1]. Frailty can actually precede adverse outcomes such as disability, long-term hospitalization, institutionalization, or death by several years [2]. In this sense, those patients classified as frail often show higher morbidity and mortality, and also increased risk of postoperative complications, after a surgical intervention [3, 4].

In the last years, the determination of frailty status has emerged as a good indicator of the individual's biological reserve. It encompasses several domains, including physical and cognitive alterations [5, 6]. Its prevalence increases with age and ranges from 5-15% in people aged 65 to 50% of elders with 85 years old or more [7]. Several scales/tools have been developed to measure frailty in the clinical setting, although no consensus has been reached to date to standardize frailty diagnosis. Nowadays, different tools focused on functional performance such as Gait Speed (GS), Timed Up and Go (TUG) and the Short Physical Performance Battery (SPPB) tests, questionnaires based on frailty phenotype such as the "FRAIL" scale [8], or scales that address the multidimensional component of frailty and can predict adverse outcomes such as the "Tilburg Frailty Indicator" [9], are increasingly implemented in primary care and hospital settings. In particular, the FRAIL scale represents a quick and easy-to-use tool that will likely become the first consensus tool for frailty diagnosis in the clinic as suggested by several groups [1, 10, 11].

Elderly, and therefore the percentage of frail individuals, is an increasing population group worldwide. This group represents a global challenge in terms of health management for all medical specialties, including geriatric oncology and neurosurgery. Brain and other nervous system tumors show a global incidence rate of 5.5-6.0 per 100,000 in Europe and 5.4 per 100,000 in North America [The Global Cancer Observatory 2020; https://gco.iarc.fr/today/data/factsheets/cancers/31-Brain-central-nervous-system-fact-sheet.pdf]. Remarkably, brain tumors are expected to increase 34.8% to 2040 globally, rising to 90.1% in patients older than 70 [The Global Cancer Observatory 2020; https://gco.iarc.fr/tomorrow/en/dataviz/tables?cancers=31&group_populations=1&age_start=14] as age is a major risk factor.

The choice of both preoperative criteria to estimate post-surgery risk and the most convenient therapeutic approach for elderly people with brain tumors are especially sensitive due to the aggressive treatments that are usually employed (craniotomy, chemotherapy, radiotherapy), and the comorbidities that these patients frequently display. Age, functional status (measured with the Karnofsky performance status-KPS score), overall health status (based on American Society of Anesthesiologists-ASA physical status classification system), neurosurgeon's clinical judgment, or a combination of them are the most common criteria to predict adverse outcomes and base treatment decisions in brain tumor older patients [12, 13]. However, a protocol refinement that includes frailty status measurement may be required since elders represent a heterogeneous group concerning their functional reserve, which represents a better prognostic factor than age alone to tolerate neurosurgical procedures [14, 15]. This is especially important considering that maximal safe surgical resection correlates with increased survival, also in elderly patients [16-18].

Oncological patients usually display more prevalence of frailty and that is associated with higher risk of treatment intolerance, post-surgery complications and mortality in a wide range of tumors [19]. In this sense, preliminary studies have started to evaluate the impact of frailty in brain tumor patients [13, 20-22], mainly by tools based on modified Frailty Index-mFI [3]. Interestingly, all of them reported that frailty increases the risk for postoperative complications and longer hospital stay not only in elders [20], but also in patients with brain tumors of all ages (≥17 years old) [13, 21, 22]. This suggests that frailty measurement could be a useful tool for preoperative risk assessment in patients that undergo neurosurgery.

In this study, we intended to determine the impact of frailty in oncological neurosurgery outcome to analyze its clinical utility as preoperative risk assessment tool to improve brain tumor patient's management in our cohort from Donostia University Hospital (Basque Country, Spain).

Materials and methods

Patients

A total of 131 patients who attended the Neurosurgery Department of the Donostia University Hospital (Guipúzcoa, Basque Country, Spain) with a diagnosis of brain tumor from May 2017 to October 2018 were enrolled in this study. Of them, five patients were not finally operated due to their poor clinical condition (low KPS, comorbidities and advanced age) and radiological assessment, eight patients died in the early postoperative period (less than two months after surgery), and one patient was misdiagnosed and finally confirmed as brain abscess. Therefore, 117 patients were considered for further analysis. In the vast majority of cases, clinical and radiological diagnosis of brain tumor was performed at the Emergency Department of the same institution through a brain computed tomography scan. The tumor histopathological diagnosis was made at the Pathology Department of the Donostia University Hospital. Those patients who underwent a non-elective surgery (*i.e.*, a scheduled surgery) as well as patients with severe cognitive and/or speech deficit that prevented a proper clinical assessment (*e.g.*, patients that had a history of stroke, Parkinson's disease or dementia, and patients unable to perform strength assessment) were excluded from our study. No age limit was considered for patient's inclusion.

This study was approved by the Clinical Research Ethics Committee of the Donostia University Hospital (PTP-FTC-2017-01) and adhered to the tenets of the Declaration of

Helsinki by the World Medical Association regarding human experimentation. All participants (and/or their relatives or guardians) read and signed an informed consent after obtaining detailed information about the study.

Data collection

Data collection was performed prospectively during 24 months (from May 2017 to May 2019). Clinical, demographic and epidemiological data were gathered during the patient's preoperative assessment as well as two months after surgery by a single neurosurgeon (P.T-P). A minimum follow-up of six months post-surgery was considered to evaluate survival. For each patient, a clinical interview including clinical exploration and anamnesis was conducted preoperatively; when possible, a relative attended the interview. All the information obtained was further verified and completed with the patient's electronic medical record using the "Osabide Global" internal clinical database from the Basque Health Service. A number of clinical variables were recorded, including functional status and autonomy (evaluated by the KPS score and Barthel Index), and frailty status (by FRAIL scale, GS and Tilburg Frailty Indicator) (compiled in Supplementary File 1). Patients were considered autonomous if KPS ≥80, Barthel Index >90 and GS ≤0.8 m/s. The postoperative evaluation included the same clinical parameters as we measured preoperatively (determining again functional status and autonomy, frailty status) and also additional variables such as surgical procedure, and early and late postoperative outcomes. Clinical data were pseudonymized to guarantee patient's privacy.

Data analysis

All patient information and measurements were recorded in a specific database. Categorical variables were expressed as absolute and relative frequencies in percentage. Continuous variables were presented as mean ± standard deviation (SD) or median and interquartile range (IQR). Statistical analysis was performed globally as well as subdividing patients in two groups: "benign" and "malignant" tumors. Chi-squared test and Fisher's exact test were performed to compare frequency data (for analytical purposes, "1-2/pre-frail" and "3-5/frail" categories for FRAIL scale, and "0-20/total", "21-60/severe" and "61-90/moderate dependency" categories for Barthel Index, were grouped). Parametric (Student's t-test) and non-parametric (Mann-Whitney U test) statistics were used for quantitative two-sample group comparisons. Kaplan-Meier method was used for survival analysis. All tests were two-sided and p-values <0.05 were considered statistically significant. Statistical analyses were performed with STATA software (v.14.0; StataCorp, College Station, TX, USA).

Results

Patient population

A full pre- and postoperative evaluation was completed for 117 patients. Of them, 59 (50.4%) were men and 58 (49.6%) women with an age range of 18-84 years old (mean age of 58.9 ± 13.9 years), being 43 (36.7%) patients older than 65 and only two (1.7%) older than 80. A total of 98 patients underwent craniotomy for resection and 19 underwent biopsy, with a six-month survival rate of 80.3% (n=94). Histologically, 70 (59.8%) patients were diagnosed with malignant tumors (47 of them with high-grade glioma and 16 with brain metastases) and 47 (40.2%) with benign tumors (mainly grade I and II meningioma followed by vestibular schwannoma). The main demographic and clinical features of patients included in this study are shown in **Table 1**.

Frailty status is more frequent before and after neurosurgery in patients with malignant tumors

We defined the frailty status of our patients prior to surgery and also during the postoperative period using three different tools (FRAIL scale, GS and Tilburg Frailty Indicator), in addition to estimating patient's autonomy with other two scores (KPS and Barthel Index) (**Table 2**). Preoperatively, the number of frail patients varied depending on the scale. Thus, we identified 53.2% (patients with benign tumors) and 72.8% (malignant tumors) pre-frail/frail individuals by FRAIL scale, 23.4% (benign) and 28.6% (malignant) by GS, and 42.6% (benign) and 41.4% (malignant) by Tilburg Frailty Indicator. In the same group of patients, the number of non-autonomous patients was 6.4% (benign) and 28.6% (malignant) by KPS, and 13.2% (benign) and 21.4% (malignant) by Barthel Index. Remarkably, patients with benign tumors were

Table 1. Main demographic and clinical features of patients enrolled in this study

Characteristic	Frequency n (%)
Total number of patients	117 (100)
Age (years)	
≤65	74 (63.3)
66-80	41 (35.0)
>80	2 (1.7)
Female gender	58 (49.6)
Benign tumor	*47 (40.2)*
Grade I and II meningioma	20 (17.1)
Vestibular schwannoma	9 (7.7)
Pituitary adenoma	5 (4.3)
Craniopharyngioma	3 (2.5)
Grade I and II glioma	3 (2.5)
Grade II oligodendroglioma	2 (1.7)
Grade I and II ependymoma	1 (0.9)
Others	4 (3.4)
Malignant tumor	*70 (59.8)*
High-grade glioma (grade III, IV and gliosarcoma)	47 (40.2)
Brain metastases	16 (13.7)
Grade III ependymoma	3 (2.5)
Primary CNS lymphoma	2 (1.7)
Radionecrosis	2 (1.7)
Obesity (BMI >30)	34 (29.1)
Active tobacco smoking	14 (12.0)
Polypharmacy	64 (55.2)
Comorbidities	*81 (69.2)*
High blood pressure	52 (44.4)
Previous cancer	48 (41.0)
Cardiovascular disease	28 (23.9)
Neurologic disease	27 (23.1)
Respiratory disease	21 (18.0)
History of falls	14 (12.1)
Surgical procedure	
Craniotomy + resection	98 (83.8)
Biopsy	19 (16.2)
Supratentorial location	97 (82.9)
Single tumor	96 (82.1)
Mortality	
≤30 days	1 (0.85)
Two months	7 (6.0)
Six months	23 (19.7)

CNS: central nervous system; BMI: body mass index.

more robust and autonomous than ones with malignant tumors by all the scales at preoperative assessment.

After postoperative evaluation, 40.4% (benign tumors) and 74.6% (malignant tumors) of patients were classified as pre-frail/frail individuals by FRAIL scale, 10.6% (benign) and 42.9% (malignant) by GS, and 19.1% (benign) and 36.5% (malignant) by Tilburg Frailty Indicator. Considering standard tools, the number of non-autonomous patients was 12.8% (benign) and 44.4% (malignant) by KPS, and 4.3% (benign) and 34.9% (malignant) by Barthel Index. The frequency of frail patients after neurosurgery was higher in those patients with malignant tumors by all the scales, with a significant decrease in their functional status too (**Table 2**).

On the other hand, from 110 patients that survived after two months and were completed for full postoperative assessment, 27 (24.5%) became pre-frail or frail after neurosurgery according to the FRAIL scale, being most of them diagnosed with a malignant tumor (n=20, 74.1%; P=0.042). A previous history of cancer also impacted the percentage of patients who worsened (59.3% vs. 36.1% of patients that improved after surgery; P=0.034) (**Table 3**). Remarkably, the mean age of patients with a better status after neurosurgery compared to those that worsened was similar (58.0 ± 14.1 vs. 58.4 ± 13.7 years) (**Table 3**), suggesting that age alone does not determine the functional status of patients after elective neurosurgery in our cohort.

Frailty status impacts patients' mortality and autonomy, but not other postoperative outcomes

Frailty status measured by FRAIL scale correlated with six-month survival, since 20 out of 23 patients who died were frail or pre-frail (P=0.002) before surgery, being all of them diagnosed with malignant tumors (**Table 4**). Tilburg Frailty Indicator and GS did raise the same results as FRAIL scale for mortality, for which frail patients according to both scores had a significantly higher six-month mortality (P=0.001 and P=0.005, respec-

Table 2. Distribution of patients according to their frailty and functional status

Scale	Preoperative			Postoperative		
	Benign tumor n (%)	Malignant tumor n (%)	*p*-value	Benign tumor n (%)	Malignant tumor n (%)	*p*-value
KPS						
≥80	44 (93.6)	50 (71.4)		41 (87.2)	35 (55.6)	
50-70	3 (6.4)	17 (24.3)		5 (10.6)	22 (34.9)	
<50	0 (0)	3 (4.3)	<0.001	1 (2.1)	6 (9.5)	<0.001
Barthel*						
100	43 (91.5)	48 (68.6)		39 (83.0)	36 (57.1)	
91-99	2 (4.6)	7 (10)		6 (12.8)	5 (7.9)	
61-90	2 (4.6)	9 (12.9)		1 (2.1)	8 (12.7)	
21-60	6 (8.6)	6 (8.6)		1 (2.1)	8 (12.7)	
0-20	0 (0)	0 (0)	0.025	0 (0)	6 (9.5)	0.005
FRAIL^						
Robust (0)	22 (46.8)	19 (27.1)		28 (59.6)	16 (25.4)	
Pre-frail (1-2)	18 (38.3)	36 (51.4)		15 (31.9)	30 (47.6)	
Frail (3-5)	7 (14.9)	15 (21.4)	n.s.	4 (8.5)	17 (27.0)	0.001
Tilburg						
Robust	27 (54.4)	41 (58.6)		38 (80.9)	40 (63.5)	
Frail	20 (42.6)	29 (41.4)	n.s.	9 (19.1)	23 (36.5)	0.010
GS						
Normal	36 (76.6)	50 (71.4)		42 (89.4)	36 (57.1)	
Abnormal	11 (23.4)	20 (28.6)	n.s.	5 (10.6)	27 (42.9)	<0.001

(*) For statistical purposes, "61-90", "21-60" and "0-20" categories were grouped as *non-autonomous* and compared to "100" and "91-99" categories, which in turn were grouped as *autonomous*. (^) For statistical purposes, "pre-frail" (1-2) and "frail" (3-5) categories were grouped as *frail* and compared to "robust" (0) category. *KPS: Karnofsky performance status; Barthel: Barthel Index; FRAIL: FRAIL scale; Tilburg: Tilburg Frailty Indicator; GS: Gait Speed; n.s.: no significant.*

tively) (**Table 4**). Regarding patients' autonomy after surgery, those patients previously classified as frail or pre-fail by FRAIL scale became less autonomous according to KPS (P=0.037) and Barthel Index (P=0.005) (**Table 5**); this difference is only due to patients with malignant tumors. Conversely, Tilburg Frailty Indicator and GS did not reach statistical significance although there is a tendency towards it (**Table 5**).

Postoperative complications (hemorrhage, cerebrospinal fluid fistula, surgical wound complications, brain ischemic stroke, reoperative surgery, and/or urinary and respiratory infections, among others) were present in 38 patients (32.5%) (Supplementary Table 1), but we did not find any association between frailty status (measured as FRAIL scale) and frequency of postoperative outcomes, even though for malignant tumors (**Table 4**). Taken together, these data point out that frailty status is associated with patients' mortality and autonomy after neurosurgery.

Discussion

In the present study, we completed an exhaustive pre- and postoperative evaluation of 117 patients who underwent an elective neurosurgery in terms of frailty status (measured as FRAIL scale, GS and Tilburg Frailty Indicator), patient's functional status and autonomy (KPS and Barthel Index), postoperative outcomes, and mortality. To the best of our knowledge, this is the first prospective study that systematically evaluates these parameters in patients with benign and malignant brain tumors separately. We found that frailty scales are more sensitive and able to identify a higher number of patients in situation of vulnerability than standard tools such as KPS or Barthel Index, regardless of tumor type (benign or malignant). Moreover, when comparing between tumor

Table 3. Main demographic and clinical features of patients that became frail and pre-frail after neurosurgery according to FRAIL scale

Characteristic	Worsening n (%)	Equal or improvement n (%)	*p*-value
Tumor type			
Benign	7 (25.9)	40 (48.2)	0.042
Malignant	20 (74.1)	43 (51.8)	
Female gender	13 (48.1)	43 (51.8)	n.s.
Age (years; mean ± SD)	58.4 ± 13.7	58.0 ± 14.1	n.s.
Obesity (BMI >30)	7 (25.9)	24 (28.9)	n.s.
Polypharmacy	15 (55.6)	42 (50.6)	n.s.
Comorbidities			
Previous cancer	16 (59.3)	30 (36.1)	0.034
Cardiovascular disease	5 (18.5)	21 (25.3)	n.s.
Neurologic disease	7 (25.9)	12 (14.5)	n.s.
Respiratory disease	5 (18.5)	13 (15.7)	n.s.
Surgical procedure			
Craniotomy + resection	23 (85.2)	71 (86.6)	n.s.
Biopsy	4 (14.8)	10 (12.2)	n.s.
KPS preop. (mean ± SD)	84.8 ± 15.5	86.1 ± 14.2	n.s.
Barthel preop.*	3 (11.1)	10 (12.0)	n.s.

(*) The number of patients corresponds to *non-autonomous* category ("61-90", "21-60" and "0-20" categories grouped). *BMI: body mass index; KPS: Karnofsky performance status; Barthel: Barthel Index; n.s.: no significant; SD: standard deviation; preop.: preoperative.*

subgroups, we observed that patients diagnosed with malignant tumors are less autonomous and frailer by all the scales considered here, as well as they are more prone to develop a frail phenotype after neurosurgery. Our results are in line with those obtained by Youngerman et al. [13], who reported that patients with benign primary brain tumors are less frail in a retrospective analysis from an American cohort. Of note, while KPS and ASA scores, together with age, represent the most extensively employed criteria to assess preoperative risk, they seem not to be good enough to evaluate patients' functional reserve and subsequent risk as demonstrated by some studies focused on evaluating frailty in older individuals who underwent an elective surgery [23, 24]. Therefore, frailty measurement would be able to identify more accurately those individuals at higher risk before neurosurgery than widely implemented predictors such as age, KPS and Barthel Index, as underscored by our study and others [13, 20].

When we compared the different frailty scales used here, we found a variable prevalence of frailty at preoperative level according to the scale employed (18-59%), which corresponds to data reported by most studies on brain tumors published until now [13, 20, 22]. This high variability was widely observed in comparative studies that consider different tools [10, 25], which again highlights the need of standardizing frailty tools' use in clinical practice, especially for non-frailty experts. Of note, the prevalence of frailty by FRAIL scale and GS, which are based on physical performance, are similar and lower than Tilburg Frailty Indicator that includes additional information about cognitive and psychosocial characteristics. These results support the use of scales based on physical performance. Our results also reinforce the idea that frailty scales such as FRAIL scale, an easy and quick tool, could be more useful than already standardized tools for preoperative assessment. In addition, the FRAIL scale is able to detect pre-frail patients, who could go unnoticed in the preoperative study using standard tools.

In our cohort, two and six-month mortality correlated with frailty status, measured by the three frailty scales independently, since most of deceased patients were frail ones, and

Table 4. Distribution of patients according to their frailty status for postoperative outcome and mortality

Postoperative outcomes				
	Benign tumor n (%)	*p*-value	Malignant tumor n (%)	*p*-value
FRAIL*				
Robust (0)	7 (31.5)		3 (15.8)	
Pre-frail (1-2)	5 (27.8)		13 (37.1)	
Frail (3-5)	4 (57.1)	n.s.	5 (35.7)	n.s.
Tilburg				
Robust	7 (35.0)		8 (28.6)	
Frail	9 (33.3)	n.s.	14 (34.2)	n.s.
GS				
Normal	11 (30.6)		16 (33.3)	
Abnormal	5 (45.5)	n.s.	6 (28.6)	n.s.
Two-month mortality				
	Benign tumor n (%)	*p*-value	Malignant tumor n (%)	*p*-value
FRAIL				
Robust (0)	0 (0)		1 (2.4)	
Pre-frail (1-2)	0 (0)		2 (3.8)	
Frail (3-5)	0 (0)	n.s.	3 (14.3)	n.s.
Tilburg				
Robust	0 (0)		0 (0)	
Frail	0 (0)	n.s.	7 (17.1)	0.021
GS				
Normal	0 (0)		3 (3.6)	
Abnormal	0 (0)	n.s.	4 (12.5)	n.s.
Six-month mortality				
	Benign tumor n (%)	*p*-value	Malignant tumor n (%)	*p*-value
FRAIL				
Robust (0)	0 (0)		2 (10.5)	
Pre-frail (1-2)	0 (0)		10 (28.6)	
Frail (3-5)	0 (0)	n.s.	10 (66.7)	0.002
Tilburg				
Robust	0 (0)		3 (10.7)	
Frail	0 (0)	n.s.	20 (47.6)	0.001
GS				
Normal	0 (0)		11 (22.5)	
Abnormal	0 (0)	n.s.	12 (57.1)	0.005

(*) For statistical purposes, "pre-frail" (1-2) and "frail" (3-5) categories were grouped as *frail* and compared to "robust" (0) category. *FRAIL: FRAIL scale; Tilburg: Tilburg Frailty Indicator; GS: Gait Speed; n.s.: no significant.*

remarkably, pre-frail and frail individuals were more prone to die independently of the frailty tool. The ability of frailty to predict postoperative mortality after neurosurgery in patients with brain tumors has been previously reported [13, 20], which together with our results reinforces the need of implementing protocols for frailty measurement during preoperative risk assessment. Moreover, preoperatively frail patients by FRAIL scale did experience higher autonomy loss after neurosurgery according to KPS and Barthel Index, which further highlights the sensitivity and efficacy of this scale. Remarkably, these results are in line with previous works in different oncological and surgical contexts where frailty implementation at preoperative level was able to optimize patient's outcome [26, 27], also with FRAIL scale [28]. Nevertheless, we did not find any association between frailty status and presence of postoperative outcomes unlike previously published reports on brain tumors [13, 20-22], although we detected the same type and rate of post-surgery complications as widely described [29, 30]. While it is true that most studies have reported a link between frailty and postoperative complications, it is important to observe that a single frailty measure alone is not always able to predict adverse outcomes and should be combined with others to identify those patients more vulnerable to surgery [31]. These differences might be due as well to several limitations to our study. First, our results might be biased by the small sample size since all previous works involved larger series (n≥260; Harland et al. [22]); indeed, a lack of statistical power might explain why frailty was not associated with postoperative complications in our cohort. In addition, the wide range of frailty scales and patients' inclusion criteria employed by the different studies (most of them focused on people aged 65 or more) limit comparisons

Table 5. Correlation between frailty (at preoperative level) and functional status (postoperative)

Preoperative frailty scale	KPS postoperative					
	Benign tumor			Malignant tumor		
	Autonomous n (%)	Non-autonomous n (%)	*p*-value	Autonomous n (%)	Non-autonomous n (%)	*p*-value
FRAIL*						
Robust (0)	21 (95.5)	1 (4.6)		13 (72.2)	5 (27.8)	
Pre-frail (1-2)	15 (83.3)	3 (16.7)		19 (57.6)	14 (42.4)	
Frail (3-5)	5 (71.4)	2 (28.6)	n.s.	3 (25.0)	9 (75.0)	0.037
Tilburg						
Robust	18 (90.0)	2 (10.0)		19 (67.9)	9 (32.1)	
Frail	23 (85.2)	4 (14.8)	n.s.	16 (45.7)	19 (54.3)	n.s.
GS						
Normal	33 (91.7)	3 (8.3)		27 (58.7)	19 (41.3)	
Abnormal	8 (72.7)	3 (27.3)	n.s.	8 (47.1)	9 (52.9)	n.s.
Preoperative frailty scale	Barthel postoperative^					
	Benign tumor			Malignant tumor		
	Autonomous n (%)	Non-autonomous n (%)	*p*-value	Autonomous n (%)	Non-autonomous n (%)	*p*-value
FRAIL*						
Robust (0)	21 (95.5)	1 (4.5)		15 (83.3)	3 (16.7)	
Pre-frail (1-2)	17 (94.4)	1 (5.6)		22 (66.7)	11 (33.3)	
Frail (3-5)	7 (100)	0 (0)	n.s.	4 (33.3)	8 (66.7)	0.005
Tilburg						
Robust	19 (95.0)	1 (5.0)		21 (75.0)	7 (25.0)	
Frail	26 (96.3)	1 (3.7)	n.s.	20 (57.1)	15 (42.9)	n.s.
GS						
Normal	34 (94.4)	2 (5.6)		32 (69.6)	14 (30.4)	
Abnormal	11 (100)	0 (0)	n.s.	9 (52.9)	8 (47.1)	n.s.

(*) For statistical purposes, "pre-frail" (1-2) and "frail" (3-5) categories were grouped as *frail* and compared to "robust" (0) category. (^) For statistical purposes, "61-90", "21-60" and "0-20" categories were grouped as *non-autonomous* and compared to "100" and "91-99" categories, which in turn were grouped as *autonomous*. *FRAIL: FRAIL scale; Tilburg: Tilburg Frailty Indicator; GS: Gait Speed; KPS: Karnofsky performance status; Barthel: Barthel Index; n.s.: no significant.*

among our cohort and others. Thus, most of previous works have used the mFI to measure frailty, which combines functional status with comorbidities' evaluation [32]. However, frailty and comorbidity are not interchangeably concepts [33] and maybe other indices such as FRAIL scale, more focused on self-reported functional performance, could be more accurate.

In conclusion, this study supports that frailty measurement could be more useful than classic preoperative risk scales such as KPS and ASA to identify patients in situation of potential vulnerability prior to neurosurgery. The identification of frail patients before surgery is especially important taking into account that frailty is considered a dynamic syndrome with potential of reversibility, at least in early and intermediate stages [1, 34]. This may open the possibility to apply surgical prehabilitation in frail and especially pre-frail patients, in order to increase the probability of postoperative success as previously suggested [35, 36]. Thus, frailty assessment to evaluate patients' functional reserve should be implemented on admission, which may contribute to optimize surgery prescription, decrease surgery-related risks, especially mortality, and improve patient's prognosis.

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Disclosure of conflict of interest

None.

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Supplementary File 1. List of clinical, epidemiological and demographic variables included in the pre- and postoperative evaluation performed in this study.

1. Age and date of birth
2. Gender
3. Radiological tumor diagnosis (by brain MRI)
4. Histopathological tumor diagnosis
5. Active pharmacotherapy: anticoagulant or antiplatelet drugs, antidiabetic drugs or insulin therapy, high blood pressure medications, lipid-lowering drugs, antidepressant drugs
6. Active tobacco smoking
7. Presence of chronic diseases
8. Type of chronic diseases: respiratory, cardiovascular, neurological, digestive, kidney, thyroid, hematologic diseases
9. History of cancer
10. Obesity (BMI >30)
11. Presence of focal neurologic signs
12. Type of focal neurologic signs: paresis, speech disorders (aphasia or dysarthria)
13. Gait abnormalities
14. Epileptic seizures
15. Preoperative assessment for frailty and functional status by FRAIL scale, Gait Speed, Tilburg Frailty Indicator, Karnofsky performance status and Barthel Index
16. Patient's psychosocial resources: family care, home care assistance, etc.
17. Preoperative corticosteroid therapy administration
18. Preoperative antiepileptic therapy administration
19. Elective neurosurgery
20. Type of surgery: craniotomy with tumor resection or biopsy
21. History of hospital admissions (in the last year)
22. Previous hospital admissions related to the current disease (brain tumor)
23. Date of last hospital admission
24. Intercurrent disease during patient's follow-up
25. Rehabilitation starting during admission
26. History of falls
27. Supratentorial or infratentorial tumor
28. Tumor location
29. Multiple tumor
30. Tumor laterality
31. Tumor location in eloquent regions (motor cortex, language areas, basal ganglia and brain stem)
32. Tumor size (mm; considering the contrast absorbing area in the preoperative brain MRI)
33. Tumor volume (cm^3)
34. Performance of brain perfusion MRI
35. Performance of diffusion MRI fiber tractography
36. Postoperative adjuvant chemotherapy
37. Postoperative adjuvant radiotherapy
38. Requirement of palliative care
39. Residual tumor in post-surgical MRI
40. Presence of postoperative complications
41. Type of postoperative complications: hemorrhage, perioperative ischemic stroke, cerebrospinal fluid fistula, surgical wound complications, urinary and respiratory infections, others
42. Reoperative surgery due to adverse outcome
43. Presence of postoperative focal neurologic signs
44. Type of postoperative focal neurologic signs: paresis, speech disorders (aphasia or dysarthria)
45. Postoperative gait abnormalities
46. Postoperative epileptic seizures
47. Postoperative assessment for frailty and functional status by FRAIL scale, Gait Speed, Tilburg Frailty Indicator, Karnofsky performance status and Barthel Index

48. Postoperative intracranial hypertension
49. Postoperative corticosteroid therapy administration
50. Postoperative antiepileptic therapy administration
51. Early tumor relapse
52. Neurological deficit recovery
53. Early death (one-month post-surgery)
54. Six-month survival post-surgery
55. Date of death

MRI: magnetic resonance imaging; BMI: body mass index.

Supplementary Table 1. Frequency and type of postoperative complications recorded in this study

Postoperative complications	Benign tumor n (%)	Malignant tumor n (%)	Global n (%)
Frequency	16 (34.0)	22 (31.9)	38 (32.5)
Hemorrhage	11 (23.4)	12 (17.4)	23 (19.8)
Brain ischemic stroke	5 (10.6)	4 (5.8)	9 (7.8)
Cerebrospinal fluid fistula	7 (14.9)	4 (5.8)	11 (9.5)
Reoperative surgery	3 (6.4)	6 (8.7)	9 (7.8)
Surgical wound complications	10 (21.3)	7 (10.1)	17 (14.7)
Systemic complications*	9 (19.1)	15 (22.0)	24 (20.7)
Residual tumor^	6 (12.8)	28 (40.0)	34 (29.1)
Early tumor relapse	0 (0)	16 (25.4)	16 (14.6)
Reoperative surgery due to early tumor relapse	0 (0)	2 (3.2)	2 (1.8)

(*) They include urinary and respiratory infections, pulmonary embolism and ileus, among others. (^) This category also includes biopsies.