CHAPTER – 16

Frailty and Brain Surgery

Background:

The judgement of whether a patient would endure a surgical procedure is usually subjective, based on the surgeon's anecdotal experience and the patient's wishes. This is especially true in people who are at higher risk, such as the elderly or those who have many comorbidities. There are few standardised, easily reproducible techniques for predicting postoperative outcomes, particularly in brain tumour patients.[1-3] Because physicians' perceptions of life expectancy differ significantly, relying solely on anecdotal information is insufficient. Although cognitive impairments have been associated to poor outcomes in older patients and patients with brain tumours, the most generally used measures to estimate preoperative risk do not account for a patient's physiologic reserve, instead focusing on existing abnormalities of discrete organ systems.[2, 5-7]

To aid in preoperative decision-making, surgeons require a standardised, verified preoperative risk assessment tool. Over the last two decades, geriatricians' research has led to a better understanding of frailty as a clinical entity.[2, 8] Frailty has been associated to a higher risk of poor outcomes in medical and surgical patients, including impairment, dementia, falls, hospitalisation or institutionalization; longer hospital stays, and increased mortality.[9] Makary et al introduced the Hopkins Frailty Score(HFS) to find a standardised, proven preoperative risk assessment tool for surgical patients (Table 1).[8] The HFS was tested on a diverse group of individuals who had major and minor general, neurologic, and urologic operations. This score was later confirmed in a group of older patients who had undergone similar general, neurologic surgery and urological procedures. [2]

Table 1: Hopkins Frailty score[8]

Criterion	Description
Shrinking	Determined by asking the patients their current weight and their weight 1 year ago. Patients who report unintentional weight loss of >10lb (> 4-5 kgs) in the last year were considered frail
Exhaustion	Determined by asking 2 questions from the CES-D scale. 1. How often in the last week did you feel this way? 2. Did you feel that whatever you did was an effort or could not get going? Patients who felt either way for >3 days in the past week was considered frail
Physical activity	The short version of the Minnesota leisure Time Activity questionnaire was used to assess frequency of physical activities. Physical activity was converted to kilocalories per week expended using a standardized algorithm (number of days physical activity took place in the past 2 weeks × duration of activity in minutes × number of kilocalories expended per minute. Men who expended <383 Kcal/week and women who expended <270Kcal/week were considered frail
Walking speed	Patients were timed while walking 15 feet (4.5 meters). Men who were <173 cms and required >7seconds or >173 cms and required 6 seconds were considered frail. Women who were <159 cms and required >7 seconds or who were >159 cms and required >6 seconds were considered frail
Grip strength	**Criteria for grip strength**

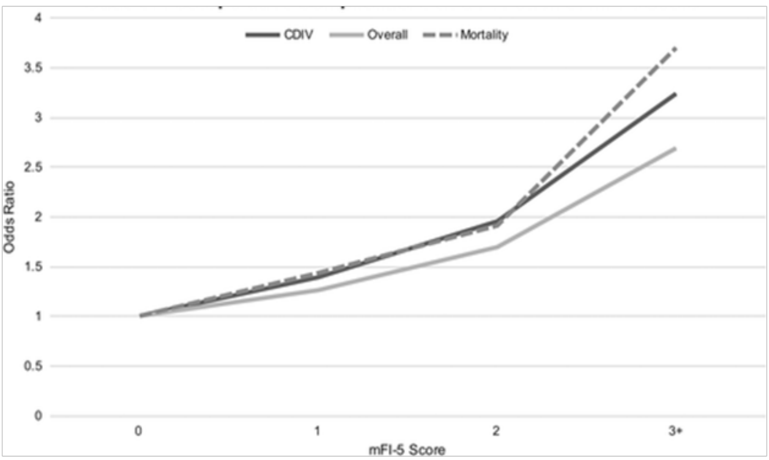
Men BMI ≤24.0 BMI =24.1-28.0 BMI >28.0	 ≤29 ≤30 ≤32
M=Women BMI ≤23.0 BMI =23.1-26.0 BMI =26.1-29.0 BMI >29.0	 ≤17 ≤17.3 ≤18 ≤21
The output is a single score that is automatically generated, providing a classification of either frail (score 3-5), pre-frail (score 1 or 2) or robust (score 0).	

Frailty and brain surgery:

Global fertility decreases and improvements in life expectancy have spurred a “demographic transition” in the world’s age distribution in recent decades.[10] The repercussions of this transition are already being felt in the world of neuro-oncology, as incidence rates of primary central nervous system (CNS) cancers such as non-malignant meningioma have risen by 3% to 5% in recent years, with substantial age-related associations. [11] In addition to this demographic transition, important changes in the field of skull base surgery have occurred in the last decade. Advances in neuroimaging, stereotactic guiding, and regional and microvascular flap repair have expanded our reach beyond the sella turcica while achieving equivalent, if not better, overall mortality, morbidity, and healthcare costs, even in the elderly. [12]

According to a population-level study by Henry RK et al, increasing frailty is related with a higher risk of overall problems, life-threatening complications, and a longer hospital stay within the 30-day postoperative period following skull base surgeries (Figure 1).[12] For each unit increase in frailty score, the risk of life-threatening systemic complications increased by 42.8%. Prior examinations of frailty in the setting of anterior cerebral fossa procedures and major head and neck surgeries in general have found similar results.

Figure 1: Odds of post-operative complications as a function of mFI-5 Score [12]



Multivariate odds of skull base surgery complications as a function of mFI-5 score. Odds ratios were given at each mFI-5 level, with score of 0 as reference, controlling for operation time, age, body mass index (BMI), American Society of Anesthesiologists (ASA) classification, wound class, and operative location.

Image source: Henry RK, Reeves RA, Wackym PA, Ahmed OH, Hanft SJ, Kwong KM. Frailty as a Predictor of Postoperative Complications Following Skull Base Surgery. Laryngoscope. 2021

Frailty and Brain tumour:

Primary and metastatic brain tumours have become more common as the population ages. [13] For informed surgical decision-making, it's critical to identify risk variables that put surgical candidates at higher risk of peri-operative morbidity or fatality. According to research, age is just a weak predictor of poor outcomes in individuals who have a craniotomy for a brain tumour.[14] Although evidence on cerebral tumour excision is far scarcer, both small institutional cohorts and larger retrospective database analyses have revealed a relationship between fragility, morbidity, and mortality. However, because the standards of neuro-oncologic care for both primary and metastatic brain tumours have changed, these assessments must be revised to match current practice.[15, 16, 17]

Understanding characteristics that may raise the risk of negative outcomes is critical for surgical decision-making and improving the informed consent procedure, which may be inadequate for older patients undergoing major surgery. Although factors such as major post-operative complications, unplanned readmissions, and mortality are intrinsically meaningful for patients and their families, it is also true that major post-operative complications can delay adjuvant therapy and impose an independent survival cost on patients in the context of oncologic care. When controlling for pertinent factors, Sastry et al found that increasing frailty is related with an increased risk of significant complication, discharge destination other than home, 30-day readmission, and 30-day mortality.[18]

When compared to non-frail patients, a multivariate analysis reveals that low- and medium-to-high frailty state provide nearly 2- and 2.5-fold greater odds of mortality. In terms of these negative outcomes, different tumour types have mixed effects; for example, metastatic tumours were not associated with a significant increase in immediate postoperative outcomes (major complication, discharge destination), but were associated with a significant increase in delayed postoperative outcomes (30-day readmission and mortality).[18]

A study by Cloney M et al suggested that frailer glioblastoma patients undergo less aggressive treatment, stay in the hospital longer, and have more complications from craniotomy for tumour excision. Frailty may be an underappreciated parameter for assessing geriatric glioblastoma patients prior to surgery.[15]

Frailty and Cerebrovascular Diseases:

Frailty appears to predispose people to the development of certain noncommunicable diseases, while chronic conditions appear to raise the likelihood of frailty in older people. [19] Frailty and chronic renal disease, atrial fibrillation, chronic obstructive pulmonary disease, anaemia, and hypertension have all been linked in this way. Frailty is also linked to polypharmacy and multimorbidity (the co-occurrence of numerous disorders in a single person). Frailty has been linked to both cardiovascular and cerebrovascular illnesses. [20, 21] In the Whitehall cohort research, cardiovascular disease risk scores were found to predict the occurrence of frailty over a 10-year period; the Framingham Stroke risk score, in particular, was related with a 35 percent increase in frailty per standard deviation increment.[22, 23, 24]

Frailty has been linked to cerebrovascular disease, according to emerging data; studies show an increased risk of frailty in people who have had a stroke, and frailty has been linked to a lower post-stroke survival rate. Frailty and prefrailty are widespread in people who have had a stroke, according to a study by Palmer K et al. [25] These findings could have clinical consequences since they highlight the importance of assessing frailty in post-stroke survivors and determining how it affects prognosis. Studies on additional forms of cerebrovascular disease, as well as better quality longitudinal research that addresses the temporal link between stroke and frailty, are needed.

Frailty and risk of stroke:

According to a recent meta-analysis of 18 studies involving 48,009 people, the prevalence of pre-frailty and frailty in people who have had a stroke is 49% and 22%, respectively.[25] Although much of the attention paid to the relationship between frailty and stroke has focused on the influence of frailty on stroke, it's also vital to evaluate the impact of stroke on frailty. Prior stroke has been demonstrated to be an essential component in the shift from robust to frail, as well as a worsening of a frailty trajectory, and neurological abnormalities following a stroke are likely to increase the phenotypic traits of frailty. More research is needed to see if this bi-directional interaction becomes a self-replicating cycle and if it may be used as a target for intervention.[26]

Figure 2: Factors influencing propagation of frailty and stroke risk[27]

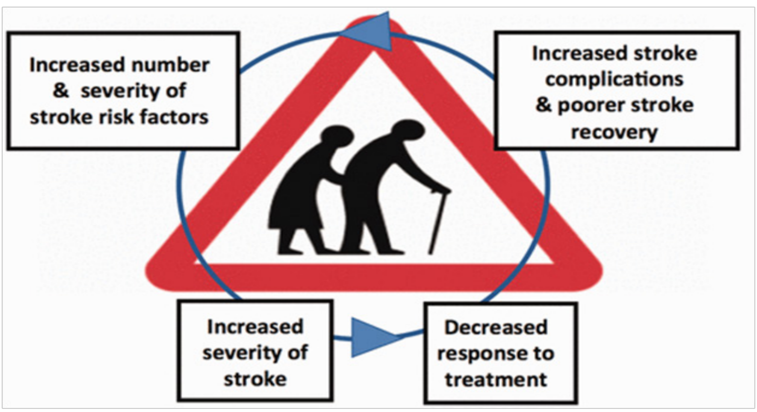


Image source: Evans NR, Todd OM, Minhas JS, Fearon P, Harston GW, Mant J, Mead G, Hewitt J, Quinn TJ, Warburton EA. Frailty and cerebrovascular disease: Concepts and clinical implications for stroke medicine. IntJ Stroke. 2021:17474930211034331.

As evaluated by the National Institute of Health Stroke Severity Scale, pre-stroke fragility is related with stroke severity in the acute situation (NIHSS).[28] In a single-center study, mediation analysis revealed that pre-stroke frailty is not directly linked to poorer outcomes, but rather that the effect is mediated by the link between frailty and stroke severity. Other studies, on the other hand, have found that even adjusting for stroke severity, the link between premorbid frailty and early outcomes remained substantial.[29] Following adjusting for age, vascular risk factors, and NIHSS, CFS was linked to increased 30-day mortality after ischemic stroke in a retrospective single-center research.[30]

Summary:

In patients undergoing surgery for brain tumour resection, frailty is an independent predictor of discharge disposition, postoperative complications, and LOS. Preoperative frailty assessment may aid neurosurgeons and patients in making more informed decisions about surgical therapy. To further investigate the use of HFS to guide clinical decisions about tumour removal and to assess the effectiveness of risk reduction methods to enhance outcomes for fragile patients, randomised controlled clinical trials will be required.

Furthermore, frailty is emerging as a significant clinical risk factor for stroke, and it is linked to a variety of negative post-stroke outcomes. Because of changing demographics and the resulting increase in frailty, the burden of frailty and its impact on cerebrovascular disease is projected to rise. Both clinical care and research are grappling with how to adequately diagnose frailty in stroke, mitigate its effects, and incorporate frailty assessment into treatment decisions.

References:

1. Partridge JS, Harari D, Dhesi JK. Frailty in the older surgical patient: a review. Age Ageing. 2012; 41:142-147.

2. Revenig LM, Canter DJ, Taylor MD, et al. Too frail for surgery? Initial results of a large multidisciplinary prospective study examining

preoperative variables predictive of poor surgical outcomes. J Am Coll Surg. 2013;217:665-670.

3. Sullivan LM, Massaro JM, D'Agostino RB Sr. Presentation of multivariate data for clinical use: the Framingham Study risk score functions. Stat Med. 2004;23:1631-1660.

4. Wilson JR, Clarke MG, Ewings P, et al. The assessment of patient life-expectancy: how accurate are urologists and oncologists? BJU Int. 2005; 95:794-798.

5. Davenport DL, Bowe EA, Henderson WG, et al. National Surgical Quality Improvement Program (NSQIP) risk factors can be used to validate American Society of Anesthesiologists Physical Status Classification (ASA PS) levels. Ann Surg. 2006;243:636-641.

6. Inouye SK, Studenski S, Tinetti ME, Kuchel GA. Geriatric syndromes: clinical, research, and policy implications of a core geriatric concept. J Am Geriatr Soc. 2007;55:780-791.

7. Robinson TN, Eiseman B, Wallace JI, et al. Redefining geriatric preoperative assessment using frailty, disability and comorbidity. Ann Surg. 2009;250:449-455.

8. Makary MA, Segev DL, Pronovost PJ, et al. Frailty as a predictor of surgical outcomes in older patients. J Am Coll Surg. 2010;210:901-908.

9. Boyd CM, Darer J, Boult C, et al. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. JAMA. 2005;294:716-724.

10. Centers for Disease Control, Prevention. Trends in aging–United States and worldwide. MMWR Morb Mortal Wkly Rep 2003; 52: 101– 104.

11. Achey RL, Gittleman H, Schroer J, Khanna V, Kruchko C, Barnholtz-Sloan JS. Nonmalignant and malignant meningioma incidence and survival in the elderly, 2005-2015, using the central brain tumor registry of the United States. Neuro Oncol 2019; 21: 380– 391.

12. Henry RK, Reeves RA, Wackym PA, Ahmed OH, Hanft SJ, Kwong KM. Frailty as a Predictor of Postoperative Complications Following Skull Base Surgery. Laryngoscope. 2021.

13. Ostrom QT, Cioffi G, Gittleman H, et al. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2012–2016. Neuro-Oncol 2019;21(5):v1–v100.

14. Seicean A, Seicean S, Schiltz NK, Alan N, Jones PK, Neuhauser D,

Weil RJ. Short-term outcomes of craniotomy for malignant brain tumors in the elderly. Cancer 2013;119(5):1058–64.

15.Cloney M, D'Amico R, Lebovic J, Nazarian M, Zacharia BE, Sisti MB, Bruce JN, McKhann GM, Iwamoto FM, Sonabend AM. Frailty in geriatric glioblastoma patients: a predictor of operative morbidity and outcome. World Neurosurg 2016;89:362–7.

16.Youngerman BE, Neugut AI, Yang J, Hershman DL, Wright JD, Bruce JN. The modified frailty index and 30-day adverse events in oncologic neurosurgery. J Neurooncol 2018;136(1):197–206.

17. Kayama T, Sato S, Sakurada K, Mizusawa J, Nishikawa R, Narita et al. Effects of surgery with salvage stereotactic radiosurgery versus surgery with whole-brain radiation therapy in patients with one to four brain metastases (JCOG0504): a phaseIII, noninferiority, randomized controlled trial. JCO 2018;36(33):3282–9.

18. Sastry RA, Pertsch NJ, Tang O, Shao B, Toms SA, Weil RJ. Frailty and outcomes after craniotomy for brain tumor. J Clin Neurosci. 2020;81:95-100.

19. Villani ER, Tummolo AM, Palmer K, Gravina EM, Vetrano DL, Bernabei R, et al. Frailty and atrial fibrillation: a systematic review. Eur J Intern Med. 2018; 56:33–8

20. Vetrano DL, Palmer KM, Galluzzo L, Giampaoli S, Marengoni A, Bernabei R, et al. Hypertension and frailty: a systematic review and meta-analysis. BMJ Open. 2018; 8:e024406.

21. Chowdhury R, Peel NM, Krosch M, Hubbard RE. Frailty and chronic kidney disease: a systematic review. Arch Gerontol Geriatr. 2017; 68:135–42.

22. Bouillon K, Batty GD, Hamer M, Sabia S, Shipley MJ, Britton A, et al. Cardiovascular disease risk scores in identifying future frailty: the Whitehall II prospective cohort study. Heart. 2013; 99:737–42

23. Llibre Rodriguez JJ, Prina AM, Acosta D, Guerra M, Huang Y, Jacob KS, et al. The prevalence and correlates of frailty in urban and rural populations in Latin America, China, and India: a 10/66 population-based survey. J Am Med Dir Assoc. 2018; 19:287–95

24. Winovich DT, Longstreth WT, Arnold AM, Varadhan R, Al Hazzouri AZ, Cushman M, et al. Factors associated with ischemic stroke survival and recovery in older adults. Stroke. 2017; 48:1818–26

25. Palmer K, Vetrano DL, Padua L, Romano V, Rivoiro C, Scelfo B, Marengoni A, Bernabei R, Onder G. Frailty syndromes in persons with

cerebrovascular disease: a systematic review and meta-analysis. Front Neurol. 2019;10:1255.

26. Lee, Y, Kim, J, Han, ES, Ryu, M, Cho, Y, Chae, S. Frailty and body mass index as predictors of 3-year mortality in older adults living in the community. Gerontology. 2014; 60: 475–482.

27. Evans NR, Todd OM, Minhas JS, Fearon P, Harston GW, Mant J, Mead G, Hewitt J, Quinn TJ, Warburton EA. Frailty and cerebrovascular disease: Concepts and clinical implications for stroke medicine. IntJ Stroke. 2021:17474930211034331.

28. Kanai, M, Noguchi, M, Kubo, H, et al. Pre-stroke frailty and stroke severity in elderly patients with acute stroke. J Stroke Cerebrovasc Dis. 2020; 29: 105346.

29. Noguchi, M, Kubo, H, Kanai, M, Nozoe, M, Shimada, S. Relationship between pre-stroke frailty status and short-term functional outcome in older patients with acute stroke – a mediation analysis. Arch Gerontol Geriatr. 2021; 94: 104370.

30. Evans NR, Wall J, To B, Wallis SJ, Romero-Ortuno R and Warburton EA. Clinical frailty independently predicts early mortality after ischaemic stroke. Age Ageing. 2020; 49(4): 588–591.