

Preoperative Frailty Predicts Postoperative Neurocognitive Disorders After Total Hip Joint Replacement Surgery

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BACKGROUND: Frailty is a reduced capacity to recover from a physiologically stressful event. It is well established that preoperative frailty is associated with poor postoperative outcomes, but it is unclear if this includes cognitive decline following anesthesia and surgery. This retrospective observational study was a secondary analysis of data from a previous study (the Anaesthesia, Cognition, Evaluation [ACE] study). We aimed to identify if preoperative frailty or prefrailty is associated with preoperative and postoperative neurocognitive disorders or postoperative cognitive dysfunction.

METHODS: The ACE study enrolled 300 participants aged ≥ 60 scheduled for elective total hip joint replacement and who underwent a full neuropsychological assessment at baseline and 3 and 12 months postoperatively. We applied patient data to 2 frailty models; both were based on an accumulation of deficits score: the reported Edmonton frail scale (REFS) and the comprehensive geriatric assessment-frailty index (CGA-FI) based on the comprehensive geriatric assessment. We calculated these 2 scores using baseline data collected from the medical history, demographic and clinical data as well as self-reported questionnaires. Some items on the REFS (3 of 18 or 17%) and the CGA-FI (37 of 51 or 27%) did not have an equivalent item in the ACE data.

RESULTS: The mean age (standard deviation [SD]) was 70.1 years (6.6) with more women (197 [66%]). Using the REFS model, 40 of 300 (13.3%) patients were classified as vulnerable, mild, or moderately frail. Using the CGA-FI model, 69 of 300 (23%) were classified as intermediate or high frailty. The REFS and the CGA-FI were strongly correlated ($r = 0.75$; $P < .01$) with 34 of 300 (11%) meeting criteria for frailty by both the REFS and the CGA-FI.

Frailty or prefrailty was associated with cognitive decline at 3 and 12 months using the REFS (odds ratio [OR], 1.51, 95% confidence interval [CI], 1.02–2.23 and OR, 2.00, 95% CI, 1.26–3.17, respectively) after adjusting for baseline mini-mental state examination (MMSE), smoking, hypertension, diabetes, history of acute myocardial infarction (AMI), and estimated intelligence quotient (IQ). Age did not modify this association. After adjusting for multiple comparisons, 3-month cognitive decline was no longer significantly associated with baseline frailty.

CONCLUSIONS: This retrospective analysis demonstrates an association between baseline frailty and postoperative neurocognitive disorders, particularly using the more extensive REFS scoring method. This supports preoperative screening for frailty to risk-stratify patients, and identify and implement preventive strategies and to improve postoperative outcomes for older individuals. (Anesth Analg 2020;131:1582–8)

KEY POINTS

- **Question:** Does preoperative frailty or prefrailty put older patients at greater risk for postoperative neurocognitive disorders?
- **Findings:** The reported Edmonton frail scale demonstrates an association between preoperative frailty and postoperative cognitive decline at 3 and 12 months.
- **Meaning:** Frailty may provide a robust assessment of risk for perioperative neurocognitive disorders in older individuals presenting for anesthesia and surgery.

GLOSSARY

ACE = Anaesthesia, Cognition, Evaluation; **aMCI** = amnesic mild cognitive impairment; **AMI** = acute myocardial infarction; **CGA-FI** = comprehensive geriatric assessment-frailty index; **CI** = confidence interval; **dNCR** = delayed neurocognitive disorder; **DSM-5** = *Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition*; **FI** = frailty index; **IADLs** = instrumental activities of daily living; **IQ** = intelligence quotient; **MCI** = mild cognitive impairment; **MMSE** = mini-mental state examination; **NART** = national adult reading test; **NCD** = neurocognitive disorders; **NSQIP** = National Surgical

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Quality Improvement Program; **OR** = odds ratio; **PND** = perioperative neurocognitive disorders; **POCD** = postoperative cognitive dysfunction; **POD** = postoperative delirium; **PVD** = peripheral vascular disease; **RCI** = reliable change index; **REFS** = reported Edmonton frail scale; **SD** = standard deviation; **VAS** = visual analog scale

Frailty is reflected by an individual's reduced capacity to recover from a stressful event, increasing the risk of poor outcomes.¹ There are 2 main frailty paradigms: the frailty phenotype model as proposed by Fried et al² and the cumulative deficit model.^{3,4} The cumulative deficit model is used more widely as it does not require specific assessment measures and can be scored from a detailed medical history.

The cumulative deficit model suggests that, as deficits accumulate in health and well-being, so do the frailty score (frailty index [FI]) and risk of adverse outcomes increases. More than 65 methods of assessing frailty have been described, each using specific features, but regardless of the tool used, the association between poor outcomes and increasing FI is robust. Frailty tools include 5–70 different frailty features.

Frailty occurs in up to 37% of community-dwelling elders and is increasingly being used as a predictor of poor outcomes following a stressful event (eg, anesthesia and surgery) in older adults.⁵ Frailty has been associated with poor postoperative outcomes including increased risk of 30-day mortality, complications, length of stay, delirium, and risk of institutionalization.^{6–9} Frailty is a stronger predictor of poor outcome than chronological age.¹

One of the major differences between the phenotype model and the accumulating deficits model is the inclusion of a cognitive function measure in some accumulating deficits models. However, the association between cognitive impairment and frailty is unclear. To date, there are very few studies investigating preoperative frailty in surgical patients and postoperative neurocognitive disorders (NCD). One study in surgical patients by Gani et al¹⁰ demonstrated an association between preoperative frailty and poor cognitive outcome following liver surgery. Cognitive changes associated with anesthesia and surgery have historically been addressed using the research diagnosis of postoperative cognitive dysfunction (POCD). Recent recommendations for perioperative neurocognitive disorders (PND) have aligned these changes with the criteria and definitions of cognitive impairment and cognitive change in the community according to the *Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition (DSM-5)*.¹¹ These recommendations define postoperative cognitive changes as postoperative mild neurocognitive disorder (mild NCD/mild cognitive impairment [MCI]) and postoperative major NCD (aligned to dementia). During transition

to newer terminology, reporting both POCD and PND outcomes will assist the interpretation of results as the new definitions become increasingly implemented.

PND are also known to be common following anesthesia and surgery, with up to 65% of patients suffering postoperative delirium and up to 15% suffering POCD at 3 months following both cardiac and noncardiac surgery.¹² Surprisingly, preoperative risk score calculators, such as National Surgical Quality Improvement Program (NSQIP),¹³ do not include screening for frailty, delirium, or cognitive impairment—all known contributors to short- and long-term poor outcomes.

The aim of this study was to retrospectively fit 2 frailty scores to data collected as part of the Anaesthesia, Cognition, Evaluation (ACE) study¹⁴ to determine the association between preoperative frailty and preoperative MCI and postoperative NCD defined as PND and POCD.

METHODS

The ACE study has previously demonstrated an association between preoperative cognitive function and POCD at 12-month follow-up. The details of this study have been previously published.¹⁴ In short, 300 older adults scheduled to undergo elective noncardiac surgery (hip joint replacement) under general anesthesia with or without regional anesthesia (spinal anesthesia) were recruited. The study was approved by St. Vincent's Melbourne human research ethics committee, and written informed consent was obtained from all subjects. Participants underwent a full neuropsychological assessment preoperatively and at 3 months and 12 months postoperatively (Supplemental Digital Content, Document, <http://links.lww.com/AA/D90>). POCD was classified using the reliable change index (RCI).¹⁵ The RCI allows the change score observed in an individual to be adjusted according to the variability expected in a control group of healthy individuals over the same time period, accounting for practice effects, time effects, and unknown effects. The calculation is described in detail in Supplemental Digital Content, Document, <http://links.lww.com/AA/D90>. When calculating the RCI, 3 assumptions of classical test theory are made:¹ the 2 error components are mutually independent and independent of the true pretest and posttest scores²; the error components are normally distributed with mean equal to zero; and³ the standard error of the difference of the 2 error components is equal for all participants.

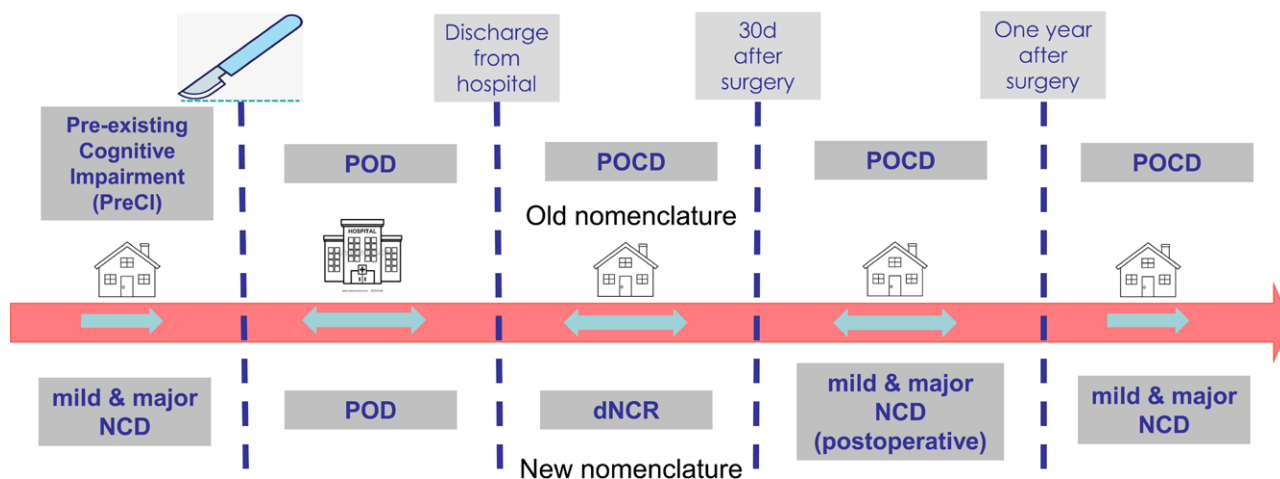


Figure 1. Nomenclature for perioperative neurocognitive disorders. dNCR indicates delayed neurocognitive disorder; NCD, neurocognitive disorders; POCD, postoperative cognitive dysfunction; POD, postoperative delirium.

Patients in the ACE study were compared against a group of patients matched for age, estimated intelligence quotient (IQ), and who had osteoarthritis but did not plan to undergo joint replacement surgery. Subjective assessment of memory or thinking decline was prospectively collected by asking patients and informants “is your memory or thinking affecting your daily life?” We calculated postoperative NCD using the RCI, subjective cognitive assessment, and instrumental activities of daily living (IADLs), according to the recent recommendations (Figure 1).¹¹ Frailty models were completed using all demographic, clinical, and medical data; patient self-reported quality of life; and IADLs, which were recorded as part of the ACE study. As this was a secondary analysis, no power calculation was undertaken. Amnesic mild cognitive impairment (aMCI) was calculated according to the recent recommendations for mild NCD.¹¹ As data were not collected at 30 days postoperatively in the ACE study, delayed neurocognitive disorder (dNCR) could not be calculated.

Reported Edmonton Frail Scale

Data from the ACE study were retrospectively fit to the reported Edmonton frail scale (REFS) as developed by Hilmer et al.¹⁶ The REFS was designed to be a validated frailty scale for use by nongeriatricians such as researchers and nurses in the acute care hospital environment. The FI uses 18 items to create a FI (REFS). Categories of frailty are classified as not frail (REFS 0–5), vulnerable (REFS 6–7), mild frailty (REFS 8–9), moderate frailty (REFS 10–11), and severe frailty (REFS 12–18). For the REFS, we identified the parameters collected as part of the ACE study which most closely aligned with each of the 18 items in the REFS, and each was assigned a score which was consistent with the scoring of the original REFS. Supplemental Digital Content, Appendix A, <http://links.lww.com/>

AA/D90, details each REFS item, the corresponding ACE variable, and the allocated score. Items on the REFS were matched to equivalent items from the ACE study data for 15 of 18 (83%) items, so the maximum score an ACE patient could achieve was 15. Items not able to be matched were whether the patient forgot to take medications and 2 items for functional performance. As a result, it is possible the level of frailty was underestimated using the REFS model.

FI Using the Comprehensive Geriatric Assessment

Data from the ACE study were also retrospectively fit to the comprehensive geriatric assessment-frailty index (CGA-FI), adapted by Krishnan et al⁸ from the CGA with 55 items, to compare the briefer REFS assessment with the longer assessment based on the CGA. As with the REFS, we identified and scored variables from the ACE database which aligned most closely with each of those in the CGA-FI model. Cutpoints have previously been established for low-frailty (CGA-FI ≤ 0.25), intermediate or moderate frailty (CGA-FI > 0.25 – 0.4), and high frailty (CGA-FI > 0.4). Supplemental Digital Content, Appendix B, <http://links.lww.com/AA/D90>, details each CGA-FI item, the corresponding ACE variable, and the allocated score. Items on the CGA-FI were matched to equivalent items from the ACE study data for 37 of 51 (73%) items. As this was an index, the denominator for each patient was the number of responses available, thus reflecting the same relative score. With fewer items, the CGA-FI is likely to underestimate frailty.

Statistical Methods

Univariable analyses were undertaken using the Spearman correlation coefficient (frailty using the REFS versus the CGA-FI) or *t* test for continuous variables (frailty versus age, estimated IQ) and the χ^2 or

Fisher exact test for dichotomous data (frailty versus comorbid factors). Separate univariable analyses were undertaken to assess associations between the REFS and the CGA-FI and cognitive outcome and all baseline demographic factors. Univariable associations with $P < .2$ were included in stepwise multivariable regression modeling. Separate multivariable logistic regression models were undertaken for associations between cognitive outcomes and REFS or CGA-FI, after adjusting for univariable associations where $P > .2$. All analyses were performed using STATA (V14 Stata Corporation, College Station, TX). A P value of $<.05$ was taken to indicate significance. The type I error rate was controlled using the Holm-Bonferroni step-down procedure for multiple comparisons.¹⁷

RESULTS

Of the $n = 300$ patients enrolled in the ACE study, all had complete baseline data to fit to the REFS and CGA-FI frailty indices. The mean age (standard deviation [SD]) was 70.1 years (6.6), with more females (197 [66%]). Table 1 details demographic and comorbid conditions at baseline.

At baseline, multidomain aMCI was observed in 46 of 300 (15%) participants. Postoperative cognitive decline was observed in 27 of 284 (10%) at 3 months postoperatively and 7 of 271 (3%) at 12 months when analyzed as POCD. When analyzed using criteria for PND, 62 of 217 (29%) and 79 of 271 (29%) met criteria for mild NCD at 3 and 12 months, respectively, and 5 of 217 (2%) and 5 of 216 (2%) for major NCD at 3 and 12 months, respectively.

For calculation of POCD, we experienced a drop out of 5% at 3 months ($n = 284$) and 10% at 12 months ($n = 271$). The clinical criteria for NCD require information from an informant as well as an assessment of

IADL, and a number of participants did not have an informant available or did not complete IADL assessment. Therefore, the numbers at 3 months ($n = 217$ or 72%) were lower than expected; although at 12 months, we were able to collect information required for NCD attribution from all participants who had POCD data.

There were no patients who met criteria for severe frailty at baseline using the REFS. One (0.5%) patient was classified as moderately frail, 12 (4%) with mild frailty, and 27 (9%) as vulnerable (prefrail) using this model. Using the CGA-FI, 231 of 300 (77%) were classified as low frailty (<0.25), 64 of 300 (21%) were classified as intermediate frailty (≥ 0.25 to <0.4), and 5 of 300 (2%) were classified as high frailty (≥ 0.4).

The REFS and CGA-FI were significantly associated (Figure 2; $r = 0.73$, 95% confidence interval [CI], 0.67–0.78; $P < .001$).

On univariable analysis, the REFS score was significantly associated with baseline anxiety, depression, fatigue, estimated IQ, aMCI, and several comorbid risk factors. Given comorbidities and a measure of cognition form part of the REFS scale, this is not surprising; therefore, due to confounding, baseline aMCI was excluded from further analysis. Separate stepwise multivariable logistic analyses that were adjusted for estimated IQ, smoking, hypertension, history of acute myocardial infarction (AMI), and diabetes demonstrated significant associations between a higher REFS score and an increased risk of POCD at 12 months (odds ratio [OR], 1.38, 95% CI, 1.01–1.90; $P = .04$) and postoperative major NCD at 3 months (OR, 1.51, 95% CI, 1.02–2.23; $P = 0.04$) and 12 months (OR, 2.00, 95% CI, 1.26–3.17; $P < .01$; Table 2; Figure 3). This association was robust using REFS as a continuous variable or when used as a categorical variable (not frail [REFS = 0–5] versus any frailty classification

Table 1. Baseline Demographics and Risk Factors

	N = 300
Age (y)	70.1 (6.6)
Sex male (%)	103 (34)
Height (cm)	166.4 (9.4)
Weight (kg)	78.5 (15.0)
Estimated IQ (NART)	111.0 (10.3)
MMSE	28.2 (1.2)
VAS depression	19.9 (23.5)
VAS anxiety	38.4 (27.2)
VAS fatigue	38.6 (28.4)
Hypertension	160 (54)
Diabetes	26 (9)
Hypercholesterolemia	115 (39)
PVD	3 (1)
History AMI	12 (4)
Smoking	144 (48)
aMCI	46 (15)

Data are provided as mean (standard deviation) or n (%).

Abbreviations: aMCI, amnesic mild cognitive impairment; AMI, acute myocardial infarction; IQ, intelligence quotient; MMSE, mini-mental state examination; NART, national adult reading test; PVD, peripheral vascular disease; VAS, visual analog scale.

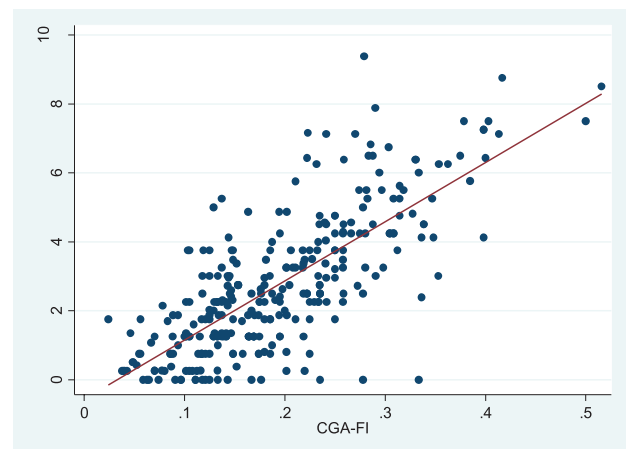


Figure 2. Scatter plot of reported Edmonton frail scale versus CGA-FI scores with linear prediction. CGA-FI indicates comprehensive geriatric assessment-frailty index.

Table 2. Multivariable Regression Model for REFS Frailty Score at Baseline and Postoperative Cognitive Outcomes

	Univariable		Multivariable			
	Test Statistic	P	OR	(95% CI)	P	Adjusted P Value
Postoperative major NCD 3 mo	$t = -3.8$	<.01	1.5	(1.02–2.23)	.04	.08
Postoperative major NCD 12 mo	$t = -2.2$	.03	2.0	(1.26–3.17)	<.01	.009
12 mo POCD	$t = -2.1$	.03	1.4	(1.01–1.90)	.04	.04

Abbreviations: CI, confidence interval; NCD, neurocognitive disorders; OR, odds ratio; POCD, postoperative cognitive dysfunction; REFS, reported Edmonton frail scale.

[REFS = 6–15]). After adjusting for multiple comparisons to avoid type I error, 3-month cognitive decline was no longer significantly associated with baseline frailty, although this adjustment may have resulted in a type II error. Patients with mild, moderate, or vulnerable frailty scores using the REFS were 9 times more likely to suffer cognitive decline at 12 months postoperatively (measured as major NCD) than those who were not frail, after adjustment (Table 3). There was no significant association observed between mild NCD at 3 months and frailty using the REFS ($z = 1.67$; $P = .09$) or at 12 months ($z = -1.24$; $P = .21$).

Similar to the REFS above, the CGA-FI score was significantly associated with all comorbid and demographic baseline variables except age. Postoperatively, univariable analyses demonstrated CGA-FI score at baseline was significantly associated with postoperative major NCD at 3 months ($t = -4.62$; $P < .001$) and POCD at 12 months ($t = -2.47$; $P = .01$). Adjusted, stepwise multivariable regression modeling revealed non-robust outcomes (CGA-FI versus POCD at 12 months: OR, 17,755.0, 95% CI, 8.31–3.79e⁷; $P = .01$). There was no significant association observed between mild NCD at 3 months and frailty using the CGA-FI score ($z = 1.94$; $P = .05$). There was also no association between mild NCD at 12 months and frailty using the CGA-FI score ($z = 0.29$; $P = .77$).

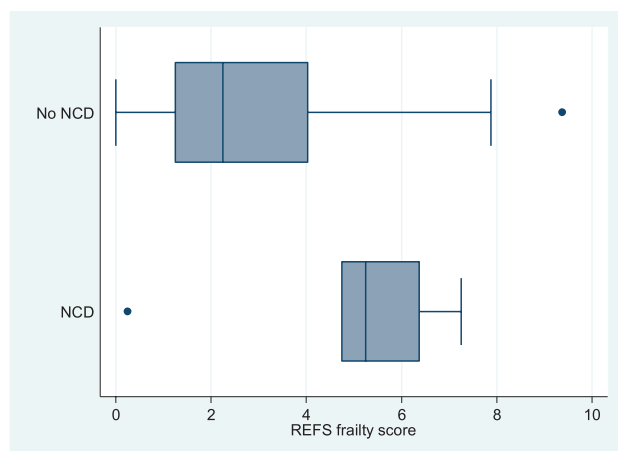


Figure 3. Neurocognitive disorder at 12 mo by REFS frailty score. NCD indicates neurocognitive disorders; REFS, reported Edmonton frail scale.

DISCUSSION

This retrospective observational analysis using data from the ACE study to score 2 frailty indices indicates that baseline frailty or prefrailty (vulnerable) is associated with medium-term cognitive decline at 3 months and long-term cognitive decline at 12 months. In particular, increasing frailty scores are significantly associated with postoperative major neurocognitive disorder (major NCD) and POCD but not with the more subtle postoperative mild NCD which is characterized by having no impact on daily function and a lesser degree of decline on objective assessments.

The most robust definition of POCD requires a decline of 1.96 SD compared to controls on ≥ 2 tests of a battery of 8–10 neuropsychological assessments.¹⁵ Although the criteria for POCD did not require a subjective or functional assessment for deficit, this objective (research) criteria reflects a large decrement in measured neuropsychological function and aligns with the objective criteria component of postoperative major NCD. Thus, it is not surprising that we observed an association between postoperative major NCD and frailty as well as an association between POCD and frailty. This association was not seen between the more subtle postoperative mild NCD. This suggests the classification of POCD using the strict RCI criteria may overlap with the classification of major NCD. Further study needs to investigate this relationship and assess the relevance of POCD literature to the more recent classifications of PND.¹¹

The prevalence of preoperative frailty in the current study is comparable to some previous studies¹⁸ but considerably lower than several other studies.^{19–21}

Table 3. Multivariable Regression Model for REFS Frailty Score as a Dichotomous Outcome and Postoperative Major NCD 12 mo

Variable	Multivariable		
	OR	OR (95% CI)	P
REFS*: categorical	9.00	(1.44–56.29)	.02
Hypertension	0.83	(0.12–5.84)	.85
Diabetes	1.88	(0.17–21.20)	.61
Estimated IQ	0.97	(0.88–1.06)	.49
Smoking	3.76	(0.39–36.00)	.25

Abbreviations: CI, confidence interval; IQ, intelligence quotient; NCD, neurocognitive disorders; OR, odds ratio; REFS, reported Edmonton frail scale.

*REFS is classified as either nonfrail (0–5) or any positive frailty score (6–15).

This may be due to the relatively healthy group of patients in the ACE study undergoing elective total hip joint replacement. Although the prevalence of frailty or prefrailty was low in the current analysis, the poor outcomes associated with frailty have been reported to be independent of the type or invasiveness of the procedure.^{18,21}

Several studies have demonstrated increased mortality following both emergent¹⁹ and elective surgical procedures¹⁸ in patients with baseline frailty, increased in-hospital and postdischarge costs associated with frailty,²² and significantly greater postoperative complications in frail or prefrail patients.

A recent review by Beggs et al²³ identified a significant body of evidence demonstrating poorer postoperative outcomes in frail or prefrail patients, regardless of the frailty tool used. This contrasts with the study executed by Sonny et al²⁰ who recently reported no association between preoperative frailty and postoperative outcomes using either the accumulation of deficits model or a phenotype frailty score. It is unclear why this report is inconsistent with the majority of literature. The study by Sonny et al²⁰ investigated hospital length of stay as the primary outcome and 30-day readmissions and complications, while most other studies have included mortality. Shinall et al¹⁸ demonstrated increased mortality among older frail patients at 30 days postsurgery—regardless of the stress level of the procedure—with what would normally be considered low and moderate stress procedures being high risk in patients with preoperative frailty.

In the case of joint replacement surgery, as for the ACE study, there is indeed the possibility that the surgery may improve frailty, as patients' activities of daily living improve with reduced pain. This requires further prospective research.

The current study suggests that frailty indices with a larger number of items may not demonstrate greater predictive power than those with fewer items. The correlation between measures is moderately high and compares with a previous study demonstrating a correlation of 0.65 between the phenotype model compared with the accumulation of deficits model.²⁴ The REFS scale with 18 items demonstrated greater predictive power for postoperative NCD than the CGA-FI with 55 items. Thus, it may be the specific items that are included rather than the number of items. We also demonstrate that medical history details can be effectively used to complete frailty scores and predict postoperative outcomes.

Future research should address frailty in a prospective manner from preoperatively to full recovery postoperatively. Investigating the possibility of frailty being modified by some types of surgery may inform strategies to improve frailty in other populations.

Further, specific to poor cognitive outcomes including delirium, it is necessary to investigate the likelihood that preoperative optimization improves outcomes for frail patients, providing evidence to support the routine implementation of "BRAIN ERAS."

LIMITATIONS

The main limitations of this study are its retrospective nature and relatively small sample size. Further limitations included that some items from the ACE study did not match precisely the items detailed in the REFS or CGA-FI scales. Additionally, we experienced a loss to follow-up of 28% at 3 months for NCD attribution which may impact how robust and generalizable our results are. A further limitation is that postoperative delirium—as a component of PND—was not measured as an outcome in these patients. Future research should assess this association prospectively and identify cut-points for frailty scores to predict PND and allow preventive strategies to be implemented.

CONCLUSIONS

This retrospective analysis demonstrates an association between baseline frailty and postoperative neurocognitive disorders, particularly using the REFS scoring method. There is an increasing number of elderly presenting for elective surgery worldwide and an increasing body of evidence demonstrating PND are the most common complications and have long-term poor impact. Therefore, an assessment of frailty at baseline using demographic and medical history may be an important and simple method of identifying and intervening with preventive strategies to ultimately reduce the incidence of PND. ■

DISCLOSURES

Name: Lis A. Evered, PhD.

Contribution: This author contributed to project conception, protocol development, manuscript preparation, data collection, and statistical analysis.

Conflicts of Interest: L. A. Evered has received compensation for lectures from Medtronic and Cogstate Ltd.

Name: Sarah Vitug, MD.

Contribution: This author contributed to protocol development and data collection.

Conflicts of Interest: None.

Name: David A. Scott, PhD.

Contribution: This author contributed to project conception, protocol development, and manuscript preparation.

Conflicts of Interest: None.

Name: Brendan Silbert, MBBS.

Contribution: This author contributed to project conception, protocol development, and manuscript preparation.

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