Frailty as a Predictor of Surgical Outcomes in Older Patients

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BACKGROUND: Preoperative risk assessment is important yet inexact in older patients because physiologic reserves are difficult to measure. Frailty is thought to estimate physiologic reserves, although its use has not been evaluated in surgical patients. We designed a study to determine if frailty predicts surgical complications and enhances current perioperative risk models.

STUDY DESIGN: We prospectively measured frailty in 594 patients (age 65 years or older) presenting to a university hospital for elective surgery between July 2005 and July 2006. Frailty was classified using a validated scale (0 to 5) that included weakness, weight loss, exhaustion, low physical activity, and slowed walking speed. Patients scoring 4 to 5 were classified as frail, 2 to 3 were intermediately frail, and 0 to 1 were nonfrail. Main outcomes measures were 30-day surgical complications, length of stay, and discharge disposition. Multiple logistic regression (complications and discharge) and negative binomial regression (length of stay) were done to analyze frailty and postoperative outcomes associations.

RESULTS: Preoperative frailty was associated with an increased risk for postoperative complications (intermediately frail: odds ratio [OR] 2.06; 95% CI 1.18–3.60; frail: OR 2.54; 95% CI 1.12–5.77), length of stay (intermediately frail: incidence rate ratio 1.49; 95% CI 1.24–1.80; frail: incidence rate ratio 1.69; 95% CI 1.28–2.23), and discharge to a skilled or assisted-living facility after previously living at home (intermediately frail: OR 3.16; 95% CI 1.0–9.99; frail: OR 20.48; 95% CI 5.54–75.68). Frailty improved predictive power ($p < 0.01$) of each risk index (ie, American Society of Anesthesiologists, Lee, and Eagle scores).

CONCLUSIONS: Frailty independently predicts postoperative complications, length of stay, and discharge to a skilled or assisted-living facility in older surgical patients and enhances conventional risk models. Assessing frailty using a standardized definition can help patients and physicians make more informed decisions. (J Am Coll Surg 2010;210:901–908. © 2010 by the American College of Surgeons)

Older patients are at increased risk for postoperative complications.[1] If a complication occurs, it can lead to a cascade of events resulting in disability, loss of independence, diminished quality of life, high health care costs, and mortality.[2] As the aging population expands, older patients are increasingly presenting for surgical evaluation.[3] Surgical decision making in this population is challenging because of the heterogeneity of health status in older adults and the paucity of tools for predicting operative risk. Commonly used predictors of postoperative complications have substantial limitations; most are based on a single organ system or are subjective, and none estimate a patient's physiologic reserves.[4] For example, the Lee and Eagle criteria account for cardiac function only,[5,6] and the popular American Society of Anesthesiology (ASA) score is determined by a subjective estimate of organ system disease and likelihood of survival.[7] Despite the widespread adoption of these scoring systems, complications in older patients remain difficult to accurately predict.

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Abbreviations and Acronyms

ASA	= American Society of Anesthesiology
AUC	= area under the receiver operating characteristic curve
LOS	= length of stay
NSQIP	= National Surgical Quality Improvement Program

There is no standardized method of measuring physiologic reserves in older surgical patients. Conceptually, decrements in reserves can determine the resilience of an older adult to recover from an operation. Frailty is increasingly recognized as a unique domain of health status that can be a marker of decreased reserves and resultant vulnerability in older patients. Frailty can be conceptualized as a global phenotype of physiologic reserves and resistance to stressors.[8,9] In nonsurgical populations, this phenotype has been associated with adverse health outcomes.[8,10-12] However, implications of frailty for surgical patients have not been studied. We hypothesized that frailty predicts operative risk in older surgical patients, and the addition of frailty to other risk models will enhance our ability to identify patients at risk for complications.

METHODS

Study design and participants

We conducted a prospective study of surgical patients age 65 years or older who presented to the Johns Hopkins Hospital anesthesia preoperative evaluation center for elective surgery during a 1-year period (June 22, 2005 to July 1, 2006). Participants underwent a standardized preoperative interview and frailty assessment by a research assistant. Demographic information, a comprehensive medical history including current prescription medications, and the patient's preoperative living situation were obtained during the interview. Data were analyzed by authors (DS, KB, JT) not involved in data collection or frailty assessment. The study was approved by the Johns Hopkins University School of Medicine institutional review board, and written informed consent obtained from all participants.

Patients were recruited on selected days of the week with days of the week rotated on a regular basis. Using this sampling method, we identified a total of 666 eligible patients on the days sampled; 21 declined participation in the study and 2 participants requested removal from the study after enrollment. We excluded patients with Parkinson disease (n = 2), previous stroke (n = 11), a Mini-Mental Status Examination score <18 (n = 2), and those taking carbidopa/levodopa, donepezil hydrochloride, or antidepressants (n = 34) because previous studies have found that these medications cause symptoms that are potentially collinear with domains of frailty.[8] Final sample size was 594.

Frailty score

We evaluated frailty based on a validated scoring system[8,9] that characterizes frailty as an age-associated decline in 5 domains: shrinking, weakness, exhaustion, low physical activity, and slowed walking speed. Detailed criteria are listed in Table 1. Each domain yielded a dichotomous score of 0 or 1 based on the following criteria:

1. Shrinking (weight loss) was defined as unintentional weight loss ≥10 pounds in the last year.
2. Decreased grip strength (weakness) was measured by having the patient squeeze a hand-held dynamometer. The strength measurement was adjusted by gender and body mass index[8,9] using a table (Table 1).
3. Exhaustion was measured by responses to questions about effort and motivation.[13]
4. Low physical activity was ascertained by inquiring about leisure time activities.
5. Slowed walking speed was measured by the speed at which patient could walk 15 feet.

Other independent variables

Information on other potentially confounding variables were collected, including age, race, gender, comorbidity (history of myocardial infarction, angina, congestive heart failure, claudication, arthritis, cancer, hypertension, diabetes, chronic obstructive lung disease, or smoking),[12] current procedure for cancer (any malignancy on a pathology report), and preoperative residence (home, nursing home, or skilled care facility). We also collected variables about operation category: major versus minor procedure (major, procedure typically requiring hospitalization; minor, procedure typically performed the same day); open versus percutaneous or minimally invasive; and intra-abdominal versus nonintra-abdominal.

Risk indices

We evaluated 4 risk models: the frailty index, American Society of Anesthesiologists (ASA) score, Lee's revised cardiac risk index, and Eagle score. Lee score (0 to 4) was determined by the presence of specific preoperative cardiac risk factors.[6] Eagle score (0 to 6) was similarly based on a standardized criteria.[5] An ASA score (1 to 6) was independently assigned by an anesthesiologist[7] blinded to the patient's frailty score.

Dependent variables

The main dependent variables (obtained from the patient's medical record) were surgical complications within 30

Table 1. Frailty Criteria

Shrinking (weight loss)	Shrinking was defined through self-report as an unintentional weight loss of ≥10 pounds in the last year.
Decreased grip strength (weakness)	Weakness was assessed by grip strength, and was measured directly with a hand-held JAMAR dynamometer (Sammons Preston Rolyan). Three serial tests of maximum grip strength with the dominant hand were performed, and a mean of the 3 values were adjusted by gender and body mass index (BMI).[8,9] Weakness was defined as an adjusted grip strength in the lowest 20th percentile of a community-dwelling population of adults 65 years of age and older. Men met the criteria for weakness if their BMI and grip strength were ≤24 and ≤29 kg; 24.1–26 and ≤30 kg; 26.1–28 and ≤31 kg; >28 and ≤32 kg, respectively. Women met the criteria for weakness if their BMI and grip strength were ≤23 and ≤17 kg; 23.1–26 and ≤17.3 kg; 26.1–29 and ≤18 kg; and >29 and ≤21kg, respectively.
Exhaustion	Exhaustion was measured by responses to the following 2 statements from the modified 10-item Center for Epidemiological Studies−Depression scale:[13] "I felt that everything I did was an effort" and "I could not get going." Subjects were asked, "How often in the last week did you feel this way?" Potential responses were: 0 = rarely or none of the time (<1 day); 1 = some or a little of the time (1–2 days); 2 = a moderate amount of the time (3–4 days); and 3 = most of the time. Subjects answering either statement with response 2 or 3 met the criteria for exhaustion.
Low activity	Physical activities were ascertained for the 2 weeks before this assessment using the short version of the Minnesota Leisure Time Activities Questionnaire, and included frequency and duration. Weekly tasks were converted to equivalent kilocalories of expenditure, and individuals reporting a weekly kilocalorie expenditure in the lowest 20th percentile for their gender (men, <383 kcal/week; women, <270 kcal/week) were classified as having low physical activity.
Slowed walking speed	Slowness was measured by averaging 3 trials of walking 15 feet at a normal pace. Individuals with a walking speed <20th percentile, adjusted for gender and height, were scored as having slow walking speed. Men met criteria if height and walk time were ≤173 cm and ≥7 seconds, or >173 cm and ≥6 seconds, respectively. Women met criteria if height and walk time were ≤159 cm and ≥7 seconds, or >159 cm and ≥6 seconds, respectively.

Each criterion is scored with a 0 or 1.

days, length of hospital stay (LOS), and discharge to a skilled or assisted-care facility. Surgical complication was defined using the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) definitions.[14] Discharge to a skilled or assisted-care facility was defined as a complication if the patient lived at home before their hospitalization for the elective surgery.

Statistical analysis

Prior work has indicated a dose−response relationship with number of frailty criteria and patient outcomes.[10,15] To ensure that frailty as a categorical variable appropriately represented the clinical association of frailty and outcomes in surgical patients, we performed an exploratory data analysis and found that risk increased stepwise across 3 categories (0 to 1, 2 to 3, 4 to 5), with patients within each category having similar odds ratios for events. Specifically, patients with a score of 2 or 3 had a similar odds ratio and patients with a score of 4 or 5 had a similar odds ratio. Using this even categorization, patients meeting 2 or 3 criteria were considered intermediately frail, and those meeting 4 or 5 were classified as frail.

NSQIP complications and discharge disposition to a skilled or assisted-living facility were modeled as binary outcomes and analyzed using logistic regression. Odds ratios resulting from these analyses were interpreted as the relative odds of a complication or discharge to nonhome when compared with the reference group. LOS was evaluated as Poisson count data and was determined to be overdispersed; as such, it was analyzed using negative binomial regression. Incidence rate ratios from these analyses were interpreted as the relative number of days in the hospital when compared with the reference group.

The association between frailty and each of the outcomes was evaluated in multiple regression models and adjusted by procedure type. To examine the potential contribution of frailty to known risk indices, regression models were constructed and included in the operation category and each of the other indices (ie, ASA, Lee, and Eagle). Each model analyzed the independent association with frailty, adjusting for the given risk index in the regression model and the difference in predictive power of each index, with and without frailty, as measured by area under the receiver operating characteristic curve (AUC).[16] AUCs were determined from the original dataset and cross-validated using a jackknife algorithm with 10 random observations deleted per iteration. To assess significance of adding frailty, p values were calculated using nonparametric methods for comparing correlated AUC curves.[17]

To examine the contribution of frailty over other risk indices and patient characteristics, adjusting for operation category, parsimonious and forced models were developed and analyzed. The appropriate functional forms of model covariates were determined by exploratory data analysis,

Table 2. Patient Characteristics (n = 594)

Characteristic	Nonfrail (n = 346)	Intermediately frail (n = 186)	Frail (n = 62)
Age, y, mean (range)	71.3 (65–94)	74.5 (65–92)	76.3 (65–94)
Female, %	67.6	52.7	41.9
Caucasian, %	83.8	82.8	83.9
ASA score, %			
1	0.9	0.5	0.0
2	63.2	44.0	41.9
3	33.6	50.0	51.6
4	2.3	5.4	6.5
Lee's score, %			
0	73.6	61.1	60.7
1	19.7	27.0	24.6
2	4.9	9.7	11.5
3	1.7	1.6	1.6
4	0.0	0.0	1.6
5	0.0	0.5	0.0
Eagle score, %			
0	41.6	19.9	17.7
1	43.1	65.6	67.7
2	11.8	12.4	9.7
3	3.5	1.6	3.2
4	0.0	0.5	1.6
Operation category, %			
Major procedure	62.4	54.3	41.9
Intra-abdominal procedure	43.1	32.6	35.5
Open procedure	62.8	67.8	64.5
Procedure for cancer	61.8	36.6	27.4
Comorbidities, %			
Myocardial infarction	7.5	8.6	8.2
Angina	7.0	8.6	8.2
Congestive heart failure	3.8	8.1	14.8
Claudication	3.2	6.5	9.8
Arthritis	15.9	22.7	29.5
Cancer	74.1	60.5	54.1
Hypertension	57.8	64.9	70.5
Diabetes	17.4	21.6	21.3
COPD	6.4	9.8	14.8
Smoking	61.0	59.7	61.3

ASA, American Society of Anesthesiologists.

and absence of collinearity was confirmed by testing variance inflation factors. Forced models included all of these variables. Parsimonious models were designed by testing nested models for a reduction in Akaike's information criterion. Model fit was tested by a Hosmer-Lemeshow goodness-of-fit test. A p value <0.05 was considered significant. All statistical analyses were performed using STATA 9.0 (Stata Corp).

Table 3. Risk of Surgical Complications by Frailty

Adjustment	Intermediately frail patients, odds ratio (95% CI)	Frail patients, odds ratio (95% CI)
Operation category*	2.02 (1.22–3.34)	3.12 (1.48–6.57)
Operation category and ASA score	2.13 (1.27–3.59)	3.15 (1.47–6.72)
Operation category and Lee score†	1.99 (1.19–3.33)	2.68 (1.23–5.87)
Operation Category and Eagle score†	1.78 (1.06–3.02)	2.72 (1.25–5.90)
Adjusted for all factors (parsimonious model)	1.97 (1.16–3.35)	2.48 (1.11–5.56)
Adjusted for all factors (forced model)	2.06 (1.18–3.60)	2.54 (1.12–5.77)

*Operation category includes operation types, major versus minor, intra-abdominal versus extra-abdominal, and open operation versus percutaneous or minimally invasive procedure.
†Lee and Eagle are cardiac preoperative risk stratification systems.
ASA, American Society of Anesthesiologists.

RESULTS

Among 594 participants, 62 (10.4%) were frail, 186 (31.3%) were intermediately frail, and 346 (58.3%) were nonfrail (Table 2). Of the 62 frail patients, 83.9% were Caucasian and 41.9% were female. Risk index scores, operative procedure categories, and comorbidities are listed in Table 1.

Frailty and postoperative complications

The unadjusted incidence of complications after minor procedures was 3.9% in nonfrail, 7.3% in intermediately frail, and 11.4% in frail patients; after major procedures, the unadjusted incidence was 19.5% in nonfrail, 33.7% in intermediately frail, and 43.5% in frail patients.

After adjusting for known risk indices and relevant patient factors, frailty remained an independent predictor of surgical complications (Table 3). Intermediately frail patients had 2.06-times higher odds (95% CI, 1.18–3.60) of complications, and frail patients had a 2.54-times higher odds (95% CI, 1.12–5.77) of complications when compared with nonfrail patients. In various adjusted models, the odds ratio for intermediately frail patients ranged from 1.78 to 2.13, and for frail patients it ranged from 2.48 to 3.15.

The association between frailty and NSQIP complications remained significant in models where frailty was compared directly with each of the other risk indices. The associated gain in predictive ability over the known indices

Table 4. Increased Length of Hospital Stay by Frailty

Adjustment	Intermediately frail patients, IRR (95% CI)	Frail patients, IRR (95% CI)
Operation category*	1.53 (1.28–1.83)	1.89 (1.43–2.48)
Operation category and ASA score	1.50 (1.25–1.79)	1.80 (1.36–2.37)
Operation category and Lee score	1.51 (1.26–1.80)	1.74 (1.32–2.30)
Operation category and Eagle score	1.44 (1.2–1.73)	1.65 (1.25–2.18)
Adjusted for all factors (parsimonious model)	1.49 (1.24–1.80)	1.67 (1.27–2.21)
Adjusted for all factors (forced model)	1.49 (1.24–1.80)	1.69 (1.28–2.23)

*See Table 2.
ASA, American Society of Anesthesiologists; IRR, incidence rate ratio.

was considerable. For example, the predictive ability of models without frailty were 63% (ASA score), 62% (Lee Score), and 68% (Eagle Score), as estimated by AUC; these increased to 70%, 67%, and 71%, respectively, when frailty was added to the model ($p < .01$).

Frailty and length of stay

Mean LOS after minor procedures was 0.7 days for nonfrail, 1.2 days for intermediately frail, and 1.5 days for frail patients; after major procedures, mean LOS was 4.2 days for nonfrail, 6.2 days for intermediately frail, and 7.7 days for frail patients.

Frailty independently predicted increased LOS in all adjusted analyses (Table 4). Intermediately frail patients had 44% to 53% longer hospital stays and frail patients had 65% to 89% longer hospital stays. As seen with NSQIP complications, the association between frailty and LOS remained significant ($p < 0.001$) in models where frailty was compared directly with each of the other risk indices.

Table 5. Risk of Discharge to a Skilled or Assisted-Care Facility

Adjustment	Intermediately frail patients, odds ratio (95% CI)	Frail patients, odds ratio (95% CI)
Operation category*	3.41 (1.26–9.20)	27.64 (9.00–84.87)
Operation category and ASA score	3.04 (1.11–8.32)	24.41 (7.88–75.64)
Operation category and Lee score	3.10 (1.13–8.52)	25.04 (7.95–78.93)
Operation category and Eagle score	3.64 (1.26–10.55)	27.56 (8.44–89.95)
Adjusted for all factors (parsimonious model)	3.34 (1.22–9.15)	25.97 (8.29–81.34)
Adjusted for all factors (forced model)	3.16 (1.00–9.99)	20.48 (5.54–75.68)

*See Table 2.
ASA, American Society of Anesthesiologists.

Frailty and discharge disposition

The unadjusted incidence of being discharged to a skilled or assisted-living facility after a minor procedure was 0.8% in nonfrail, 0% in intermediately frail, and 17.4% in frail patients; after major procedures, the unadjusted incidence was 2.9% in nonfrail, 12.22% in intermediately frail, and 42.11% in frail patients.

In an adjusted model, frailty independently predicted the odds of being discharged to a skilled or assisted living facility (Table 5). Intermediately frail patients had 3.16-fold higher odds (95% CI, 1–9.99) of being discharged to a skilled or assisted-living facility. As seen with complications and LOS, the association between frailty and discharge disposition remained significant ($p < 0.001$) in models where frailty was compared directly with each of the other risk indices (Table 6). The predictive ability of models without frailty were 71% (ASA score), 67% (Lee Score), and 66% (Eagle Score); these increased to 81%, 80%, and 76%, respectively, on adding frailty to the risk prediction ($p < 0.01$).

Table 6. Receiver Operating Characteristics Area under the Curve by Predictor

	Surgical complication, ROC statistic				Discharge to an assisted or skilled nursing facility, ROC statistic			
Predictor	Alone	Frailty added	Contribution of frailty	p Value*	Alone	Frailty added	Contribution of frailty	p Value*
ASA score (original dataset)	0.708	0.748	0.040	0.040	0.783	0.869	0.086	0.008
ASA score (cross-validation)	0.626	0.699	0.073	<0.001	0.712	0.807	0.095	0.009
Lee score (original dataset)	0.715	0.740	0.025	0.144	0.753	0.862	0.109	0.008
Lee score (cross-validation)	0.618	0.669	0.051	0.004	0.669	0.795	0.126	0.004
Eagle score (original dataset)	0.732	0.753	0.021	0.61	0.768	0.865	0.097	0.009
Eagle score (cross-validation)	0.678	0.714	0.036	0.003	0.661	0.759	0.098	0.013

*p Values were calculated using nonparametric methods.
ASA, American Society of Anesthesiologists; ROC statistic, receiver operating characteristic area under the curve.

Frailty and predictive power

As expected, we found that the ASA, Lee, and Eagle scores predicted surgical complications and discharge to an assisted or skilled nursing facility. However, frailty further increased the power of these risk indices. Demonstrated as the added AUC (Fig. 1), frailty increased the area for each index in predicting complications (ASA, 0.07; Lee, 0.05; Eagle, 0.04) and discharge to a skilled or assisted-living facility (ASA, 0.10; Lee, 0.13; Eagle, 0.10) (Table 3).

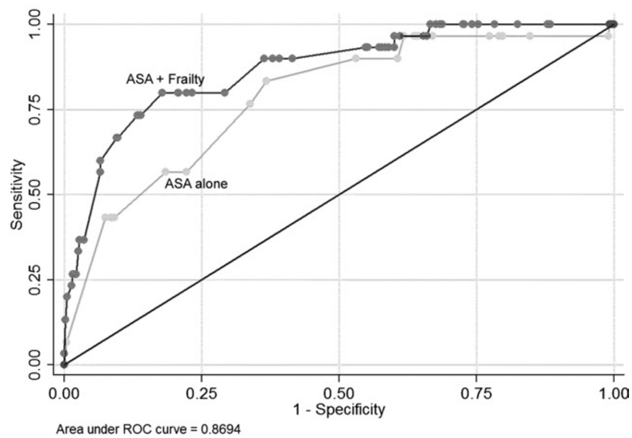
DISCUSSION

For years, it has been subjectively recognized that some older patients might not have the physiologic reserve to withstand an operation. However, physicians have lacked standardized definitions for this domain of risk. As a result, the science of this vulnerability has not been advanced. Using a validated scoring system, we found that a preoperative characterization of frailty predicted surgical outcomes and augmented other risk assessment models.

Frailty might help explain why some older patients recover better than expected and others fare worse than expected. This phenomenon is believed to be a phenotype that identifies those with decreased physiologic reserves in multiple organ systems. This phenotype has been associated with dysregulation of multiple physiologic systems, including a generalized inflammatory state,[18] dysregulated cortisol,[15] altered heart rate variability, changes in hormonal status,[19] and decreased immune function.[20,21] It has been posited that each criterion of the phenotype is related in a vicious cycle of dysregulated energetics,[8] a cycle that spirals downward with decreasing adaptive capacity. The frailty syndrome is a clinically apparent and now measurable manifestation of these changes after a certain threshold point is crossed.

Although this is the first study of frailty and surgical outcomes, the scale has been linked to poor outcomes in medical patients. Frailty in nonsurgical populations has been associated with mortality, morbidity, falls, activities of daily living disability, and hospitalization.[8-11] In addition, cardiovascular disease,[8,22,23] insulin resistance,[24] and female gender have been associated with frail health. We found that frailty had a stronger influence on surgical outcomes after major surgical procedures compared with minor procedures. This finding supports the concept of frailty as a capacity to adapt to stressors.[8,25]

Currently, approximately half of all operations in the United States are performed in patients older than 65 years of age. Based on recent population projections, it is estimated that a surgeon's average volume will increase by 14% to 47% from the year 2000 to 2020 because of elderly patients.[3] This patient population is at high risk for mor-



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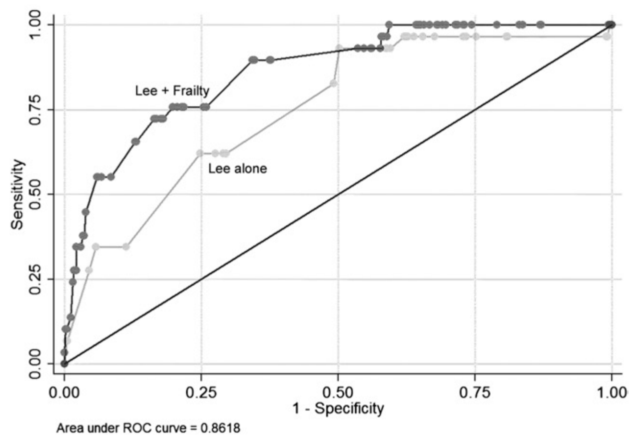

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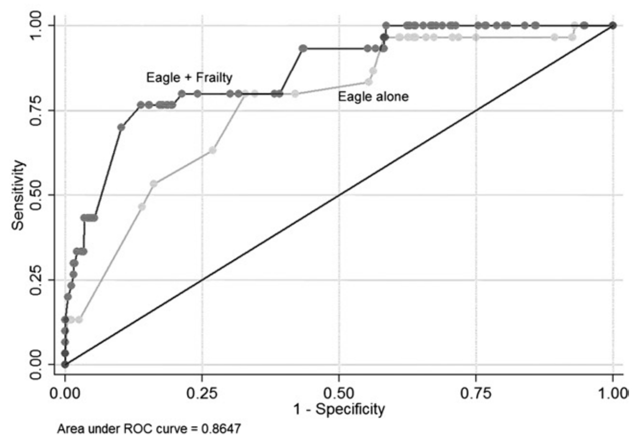

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Figure 1. (A) American Society of Anesthesiologists (ASA), (B) Lee, and (C) Eagle risk indices. Each panel shows the area under the receiver operator characteristics (ROC) curve to demonstrate the ability of the specific risk index to predict surgical complications and discharge to an assisted or skilled nursing facility. Frailty was added to the risk index scoring to demonstrate the combined ability of these indices to predict discharge disposition.

bidity, mortality, and increased costs. Khuri and colleagues demonstrated that postoperative complications were more predictive than preoperative risk factors in determining survival.[26]

A fundamental tenet of geriatric medicine is that standard indications for medical interventions might not be generalizable to older patients because physiologic changes from aging, potentially exacerbated by multiple morbidities, can alter the risk-to-benefit analysis. Medical care must be based on each patient's personal goals, physiologic status, long-term prognosis, and risk-to-benefit ratio. Our study suggests that the frailty index can provide additional information to help physicians make more accurate predictions and help patients make more informed and personal choices.

We found that the described scoring system was feasible to perform in a busy surgical practice, taking 10 minutes to conduct the assessment. Once a patient has been identified as frail, physicians can integrate frailty into their discussions of the risks and benefits of surgery. As the phenotype becomes better studied, patients can benefit from interventions to reduce risk, such as preoperative conditioning, nutrition, or even pharmacological therapy. At a minimum, providers will be alerted to the special needs and risks of older surgical patients.[10,27-30] In the postoperative period, it might be possible to decrease the risk of complications in frail patients through closer monitoring and attention to hydration, nutrition, and mobilization. Reducing postoperative complications in older patients is important because complications have been shown to increase 30-day mortality by 26% in patients aged 80 and older.[2] Well-designed clinical studies will be needed to develop targeted risk-reduction strategies for frail patients.

We recognize several study limitations. First, we only evaluated short-term outcomes and did not evaluate the impact of frailty on long-term functional outcomes and quality of life. In addition, we did not include laboratory values, such as complete blood count or albumin, which might help predict poor outcomes. Second, our results at an academic medical center might not be generalizable beyond similar patients. Third, because providers were blind to the frailty results, we do not know the impact that knowledge of frailty status could have on care. Nevertheless, our study has notable strengths. It is the first known study to evaluate the association between preoperative frailty and surgical outcomes. In addition, this study quantifies the common perception among clinicians that patients with low reserves are at increased risk for surgical morbidity.

In summary, frailty is common in older surgical patients, and is independently associated with a greater risk for postoperative complications, increased LOS, and discharge to an assisted or skilled nursing facility. In addition, the frailty index strengthened the predictive ability of other commonly used operative risk models. Broad use of the frailty index can help inform clinical decisions among patients and clinicians.

Author Contributions

Study conception and design: Makary, Segev, Pronovost, Syin, Bandeen-Roche, Takenaga, Holzmueller, Fried
Acquisition of data: Syin, Patel, Takenaga
Analysis and interpretation of data: Makary, Segev, Pronovost, Bandeen-Roche, Tian, Fried
Drafting of manuscript: Makary, Segev, Syin, Takenaga, Holzmueller
Critical revision: Pronovost, Segev, Makary, Fried

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