Assessment of Morbidity and Mortality After Esophagectomy Using a Modified Frailty Index

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Background. Esophagectomy is associated with significant morbidity and mortality. This retrospective study examined use of a modified frailty index as a potential predictor of morbidity and mortality in esophagectomy patients.

Methods. National Surgical Quality Improvement Program Participant Use Files were reviewed for 2005 through 2010. Patients undergoing esophagectomy were selected based on CPT codes. A modified frailty index with 11 variables was used to determine correlation between frailty and postesophagectomy morbidity and mortality. Data were analyzed using χ² test and logistic regression.

Results. A total of 2,095 patients were included in the analysis. Higher frailty scores were associated with a statistically significant increase in morbidity and mortality. A frailty score of 0, 1, 2, 3, 4, and 5 had associated morbidity rates of 17.9% (142 of 795 patients), 25.1% (178 of 710 patients), 31.4% (126 of 401 patients), 34.4% (48 of 140 patients), 44.4% (16 of 36 patients), and 61.5% (8 of 13 patients), respectively. A frailty score of 0, 1, 2, 3, 4, and 5 had associated mortality rates of 1.8% (14 of 795 patients), 3.8% (27 of 710 patients), 4% (16 of 401 patients), 7.1% (10 of 140 patients), 8.3% (3 of 36 patients), and 23.1% (3 of 13 patients), respectively. When using multivariate logistic regression for mortality comparing age, functional status, prealbumin, emergency surgery, wound class, American Society of Anesthesiologists score, and sex, only age and frailty were statistically significant. The odds ratio was 31.84 for frailty (p = 0.015) and 1.05 (p = 0.001) for age.

Conclusions. Using a large national database, a modified frailty index was shown to correlate with post-esophagectomy morbidity and mortality. Such an index may be used to aid in improving risk assessment and patient selection for esophagectomy.


A sixfold increase in the incidence of esophageal cancer has occurred in the United States during the past three decades [1]. By 2030, approximately 5% of the US population will be octogenarians, with 70 million older than 65 years [2], which makes preoperative risk assessment and patient selection for specific types of surgery increasingly more important. Esophagectomy is associated with significant morbidity and mortality, and preoperative risk assessment and patient selection remain a challenge. Frailty, a standardized measure of physiologic reserve, has been used more frequently in attempts to predict morbidity and mortality in the preoperative setting.

Frailty is usually measured by combining the medical history, physical examination, and assessment of physical capabilities, such as walking speed and grip strength [3]. As a state of increased vulnerability to adverse outcomes, frailty is commonly associated with the elderly and identified by decreased reserves in multiple organ systems, such as declining cognition, physical ability, and health. Frailty can be related to disease, lack of activity, inadequate nutrition, stress, and the physiologic changes associated with aging [4]. Fried and colleagues [5] first defined the frailty phenotype in 2001 as the presence of three or more of the following symptoms: unintentional weight loss of more than 10 pounds (4.5 kg) in the past year, self-reported exhaustion, weakness as measured by grip strength, slow walking speed, and low physical activity. The phenotype was independently predictive of incidence of falls, disability, worsening mobility or activities of daily living, hospitalization, and death [5]. Makary et al [6] used the frailty phenotype, finding that frail patients undergoing elective general surgical procedures were at high risk for morbidity and discharge to a skilled-care or assisted-living facility. If frailty were able to be quantified, interventions and need for institutional care could be planned and risk of mortality predicted preoperatively.

The Canadian Study of Health and Aging (CSHA) developed a frailty index (FI) based on history and physical examination. Using a 70-item scale, the CSHA-FI is the ratio of the number of items present to the total number of items assessed [7]. This model is based on the theory of “accumulating deficits” and is known to predict survival [8]. A modified frailty index (mFI) has been...
Material and Methods
The NSQIP Participant Use Files were reviewed for 2005 through 2010. The NSQIP is the American College of Surgeons’ quality improvement program with a nationwide, validated, outcomes-based data set. Approximately 237 hospitals currently participate in the NSQIP. The database incorporates more than 240 variables including demographics, surgical profiles, comorbidities, and preoperative and intraoperative variables. For example, the 2009 participant use file contains 336,190 cases with 30-day acuity-adjusted mortality and morbidity with an interrater reliability of greater than 90%. The study was approved by the institutional review board, and individual consent was waived because patients were not identified in the study.

For this study, patients who underwent esophagectomy were selected based on current procedural terminology (CPT) codes 43101 through 43123. The CSHA-FI was consolidated into the mFI, which consisted of 11 variables. The 11 variables were selected because they were present in both the CSHA-FI and in the measured NSQIP preoperative variables. The 16 preoperative variables collected in the NSQIP database were mapped to the 11 assessed in the CSHA-FI to create the mFI (Table 1). Previous literature has shown that frailty indices with as few as 10 variables are reliable [11]. The mFI was used to determine the correlation between frailty and post-esophagectomy morbidity and mortality. The mFI was calculated by the number of variables present divided by the total possible, ie, an mFI of 0.09 is equivalent to having one variable (1/11).

Categorical variables were compared using the \( \chi^2 \) test. Outcomes measured included postoperative pneumonia, prolonged ventilation (>48 hours), reintubation, shock, myocardial infarction, deep vein thrombosis, cardiac arrest, and Clavien-Dindo IV complications [12] (Table 2), and death. Age, functional status, prealbumin, emergency surgery, wound class, American Society of Anesthesiologists score, sex, race, and mFI were placed in a multivariate

<table>
<thead>
<tr>
<th>Table 1. Variables of the Canadian Study of Health and Aging Frailty Index Mapped Onto the National Surgical Quality Improvement Program Preoperative Risk Factors</th>
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</thead>
<tbody>
<tr>
<td><strong>CSHA-FI</strong></td>
</tr>
<tr>
<td>Changes in everyday activity</td>
</tr>
<tr>
<td>Problems with getting dressed</td>
</tr>
<tr>
<td>Problems with bathing</td>
</tr>
<tr>
<td>Problems with carrying out personal grooming</td>
</tr>
<tr>
<td>Problems cooking</td>
</tr>
<tr>
<td>Problems going out alone</td>
</tr>
<tr>
<td>History of diabetes mellitus</td>
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<tr>
<td>Lung problems</td>
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<tr>
<td>Respiratory problems</td>
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<tr>
<td>Congestive heart failure</td>
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<tr>
<td>Myocardial infarction</td>
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<tr>
<td>Cardiac problems</td>
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<tr>
<td>Arterial hypertension</td>
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<tr>
<td>Clouding or delirium</td>
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<tr>
<td>History relevant to cognitive impairment or loss</td>
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<tr>
<td>Family history relevant to cognitive impairment</td>
</tr>
<tr>
<td>Cerebrovascular problems</td>
</tr>
<tr>
<td>History of stroke</td>
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<tr>
<td>Decreased peripheral pulses</td>
</tr>
</tbody>
</table>

CSHA-FI = Canadian Study of Health and Aging frailty index; COPD = chronic obstructive pulmonary disease; NSQIP = National Surgical Quality Improvement Program.
logistics regression model with mortality as the outcome. Tests were considered significant at a probability value of less than 0.05. Analyses were performed using SPSS 20 (IBM Corp, Armonk, NY).

Results
A total of 2,095 patients were included in the analysis. The number of patients corresponding to each mFI is shown in Table 3. Higher frailty scores were associated with a statistically significant increase in morbidity and mortality (Table 4). For Clavien 4 complications, an mFI of 0, 0.09, 0.18, 0.27, 0.36, and 0.45 had associated rates of 17.9% (142 of 795 patients), 25.1% (178 of 710 patients), 31.4% (126 of 401 patients), 34.4% (48 of 140 patients), 44.4% (16 of 36 patients), and 61.5% (8 of 13 patients), respectively. For postoperative respiratory complications, we assessed postoperative pneumonia, reintubation, and prolonged ventilation. We found as the mFI increased so did the respiratory complication rate. For postoperative pneumonia, cases increased from 13.2% (175 of 710 patients) to 30.8% (286 of 910 patients) as the mFI increased. For reintubation, the rate increased from 12.3% (175 of 710 patients) to 22.2% (184 of 820 patients). For prolonged ventilation, the rate increased from 13% (127 of 970 patients) to 30.8% (286 of 910 patients) as the mFI increased.

For postoperative cardiovascular complications we looked at cardiac arrest, myocardial infarction, deep vein thrombosis, and shock. Again, as the mFI increased so did the rate of cardiac complications. For cardiac arrest the overall rate was 2% (41 of 2,095 patients), with a rate of 1.3% (10 of 795 patients) with an mFI of 0, and 7.7% (13 of 13 patients) with an mFI of 0.45. The rate of myocardial infarction increased from 0.3% (2 of 795 patients) with an mFI of 0, to 7.7% (1 of 13 patients) with an mFI of 0.45. The overall rate of deep vein thrombosis was 5.3% (112 of 2,095 patients). It was 4.4% (35 of 795 patients) with an mFI of 0, and 15.4% (2 of 13 patients) with an mFI of 0.45. Postoperative shock increased from 6% (48 of 795 patients) to 23.1% (3 of 13 patients) for an mFI of 0 to 0.45.

For mortality, an mFI of 0, 0.09, 0.18, 0.27, 0.36, and 0.45 had associated rates of 1.8% (14 of 795 patients), 3.8% (27 of 710 patients), 4% (16 of 401 patients), 7.1% (10 of 140 patients), 8.3% (3 of 36 patients), and 23.1% (3 of 13 patients), respectively. Renal insufficiency, pulmonary embolism, and urinary tract infection were not found to be statistically significant.

One hundred sixty-seven patients had chemotherapy within 30 days of surgery, 556 patients had radiotherapy within 90 days of surgery, and 50 cases were emergencies. Of the patients who had chemotherapy, the mortality rate was 2.5% (4 of 157 patients), compared with 3.6% (69 of 1,938 patients) who did not have chemotherapy. There was no statistically significant difference. There was also no statistically significant difference in Clavien 4 complications (21% in patients who underwent chemotherapy and 25% in those who did not). Of the patients who had radiotherapy, the mortality rate was 3.4% (19 of 556 patients), compared with 3.5% (54 of 1,539 patients) who did not have radiotherapy (not statistically significant). For Clavien 4 complications, the rate was 22.8% (127 of 556 patients) in patients who underwent radiotherapy and 25.4% (391 of 1,539 patients) in those who did not have radiotherapy.

For multivariate logistic regression we chose variables known to increase morbidity and mortality from previous literature. Using mortality as the outcome, we compared

Table 3. Distribution of Patients According to Modified Frailty Index and Number of Variables Present

<table>
<thead>
<tr>
<th>mFI</th>
<th>No. of Variables Present</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>795</td>
</tr>
<tr>
<td>0.09</td>
<td>1</td>
<td>710</td>
</tr>
<tr>
<td>0.18</td>
<td>2</td>
<td>401</td>
</tr>
<tr>
<td>0.27</td>
<td>3</td>
<td>140</td>
</tr>
<tr>
<td>0.36</td>
<td>4</td>
<td>36</td>
</tr>
<tr>
<td>0.45</td>
<td>5</td>
<td>13</td>
</tr>
</tbody>
</table>

mFI = modified frailty index.
age, functional status, prealbumin, emergency surgery, wound class, American Society of Anesthesiologists score, race, and sex, and found only age and frailty were statistically significant. For frailty the odds ratio was 31.84 ($p = 0.015$) and for age the odds ratio was 1.05 ($p = 0.001$).

**Comment**

Frailty is an emerging concept to be explored as a risk factor for patients undergoing esophagectomy. Risk stratification for thoracic surgery does not consistently identify frail patients primarily because of the inability to assess age-related decline. As the population ages and the incidence of esophageal cancer increases, identifying frail patients at high risk for postoperative morbidity and mortality is becoming a greater challenge. Assessing the effect of age on treatment decisions and outcomes and developing methods to assess which subset of older patients is appropriate for standardized treatment approaches will be increasingly important [13].

Previously, individual studies have suggested that elderly patients encounter more surgical complications, exhibit a higher rate of morbidity and mortality, and experience a poorer long-term outcome after esophagectomy [14]. However, other studies have demonstrated that esophagectomy can be performed safely in octogenarians who have good underlying cardiac and lung function [15]. Further reports have concluded that patients older than 70 years must not be presumed unsuitable for major cancer operations including esophagectomy if medical comorbidities can be identified and well controlled during the perioperative period [16]. Age is currently a key discriminating factor for undergoing esophagectomy in many cancer centers; however, the validity of using age as a single factor for assigning therapy is subject to debate [13]. Interestingly, multivariate logistic regression analysis in our study showed that with mortality as the outcome, frailty had a much higher odds ratio than age (31.84 compared with 1.05).

In the future, mFI could potentially become an essential component of counseling patients for esophagectomy. Selecting appropriate patients for surgical resection is critical because the surgical trauma caused by esophagectomy is greater than that caused by any other general surgical operation. It often involves the chest, abdomen, and neck, and may cause postoperative respiratory complications and immune depression, resulting in the inhibition of host immunity against postoperative infections [17, 18]. Respiratory morbidity remains the most common serious complication after esophagectomy [19–21], and the incidence of major respiratory complications can reach 30% or higher [22]. We found that as the mFI increased so did the respiratory complications.

The mFI used in our study was developed from variables that are available in a simple patient encounter or from most inpatient and outpatient documents. Although we did not use all the items of the CSHA-FI in our study, Rockwood and colleagues [23] previously found that any 10 items on the CSHA-FI have a similar predictive value for frailty. In addition, the theory of “accumulating deficits” corresponds well to a previous study demonstrating that the cumulative effects of existing comorbidities are greater than what would be predicted if the effects of these comorbidities were simply additive [24]. It has also been documented in the NSQIP that fewer data points are needed to provide equivocal risk assessment [25].

As expected, the morbidity and mortality rates in our study increased as the mFI increased. Our study shows that the simple method to calculate mFI can help surgeons assess complication and mortality rates for esophagectomy. We consider this a promising start, and through prospective validation, the mFI could potentially become an essential component of counseling patients for esophagectomy. We were able to compare the mFI with the American Society of Anesthesiologists score in our multivariate logistic regression, but unfortunately we are unable to compare it with other standard measures of risk, such as the Charlson comorbidity index, because the score cannot be calculated with the NSQIP data.

Our study has several limitations. First, the mFI has not been validated in a prospective trial. Except for functional status and impaired sensorium, the matched NSQIP variables are comorbid conditions. Frailty and comorbidity have significant overlap, and it remains largely unanswered, especially among geriatricians, whether comorbidities are predictors of increased operative risk or indicators of frailty per se. Second, the NSQIP data do not differentiate between pathology (squamous versus adenocarcinoma) and surgical modality (minimally invasive esophagectomy, transhiatal, McKeown, and such). Third, well-established, common tests for preoperative thoracic surgery risk stratification, such as arterial blood gas and pulmonary function tests, are not available in the NSQIP database, and therefore we were unable to include these variables in our analysis.

In conclusion, our study demonstrates that the mFI may help to identify patients preoperatively who may be at high risk for morbidity and mortality after esophagectomy. This simplified mFI is readily calculated, although its validity needs to be confirmed in a prospective trial. Assessment of frailty should become an essential component of thoracic surgery risk stratification. With an expected increase in the age of patients undergoing esophagectomy, preoperative selection will become increasingly important in minimizing postoperative complications and prolonged institutionalization.

**References**

5. Fried LP, Tangen CM, Walston J, et al; Cardiovascular Health Study Collaborative Research Group. Frailty in older adults:

DISCUSSION

DR THOMAS VARGHESE (Seattle, WA): The original frailty index includes unintentional weight loss, but the modified does not; is that correct?

DR HODARI: Correct.

DR VARGHESE: Why was the modified index then used for this particular patient population? Since in esophageal cancer, dysphagia and unintentional weight loss are significant contributors to the comorbidities these patients have, wouldn’t you think that it would be important to include that?

DR HODARI: The modified frailty index was created by mapping variables in NSQIP (National Surgical Quality Improvement Program) to those found in the Canadian Frailty Index, and unintentional weight loss was not available in the NSQIP data.

DR MARK KRASNA (Neptune, NJ): I enjoyed the presentation. My comments actually are really more about the methods, not any of your findings.

This is actually going to be the third time in the meeting that we’re going to be discussing data as it relates to thoracic surgery from NSQIP data. Just last week at the GI Cancer Symposium there was a paper talking about a very high mortality after esophagectomy based on NSQIP data.

My question to you, and perhaps, if I may, from the moderators to the audience, is, how many thoracic surgeons participate in the NSQIP data? In the last paper, when we were looking at the STS (Society of Thoracic Surgeons) database, I think we have a robust series of “esophagectomists” who are thoracic surgeons and we know what those data are. But, for instance, the data represented last week from NSQIP was primarily nonthoracic esophageal surgeons with a much higher mortality and morbidity.

I know personally I’m not an NSQIP participant and I don’t know if many people in this room are. So do you know how many of these were thoracic surgeons?

DR HODARI: I know that in the NSQIP database, the majority of esophagectomies are performed by general surgeons. I don’t know the exact number, but the majority are general surgeons.

DR K. ROBERT SHEN (Rochester, MN): We submit our data to NSQIP.

DR KRASNA: How many people or their hospitals in this room belong to NSQIP? (Show of hands.)

So it’s about half. I would just say perhaps it’s worthwhile to readdress this based on an STS database, because I think you may actually find some change.

DR HODARI: Yes, that’s what I think we’re going to do next is look if we can use our modified frailty index with the STS data and see if we find similar results.

DR ANTOON LERUT (Leuven, Belgium): Just one question, perhaps I missed it in your presentation. What is the definition of mortality, is that 30-day mortality?
DR HODARI: The mortality is 30-day mortality.

DR LERUT: Because I think it’s worthwhile, maybe it’s not in the database, to look at these figures at 90-day mortality. Because, of course, the high-risk patients they die within 30 days, but there is a big increase of mortality almost doubling at 90 days and that, of course, makes an imbalance if you look at the 30-day mortality.

DR BRYAN MEYERS (St. Louis, MO): I enjoyed your paper as well.

There are a couple of challenges in evaluating patients. Number one is the challenge of whether you just operate on them or you offer them induction therapy and then reconsider them. And I find in my own personal practice, it’s hard sometimes to say no altogether. So if somebody is T3 or N1, I’ll let them get some induction therapy and then get them back to reevaluate them.

I’d be particularly interested in this type of analysis being applied then, because a lot of times they haven’t really been improved by that process and maybe it just shows that I’ve procrastinated in making a difficult decision and probably made it even harder by putting it off until after their induction therapy. Do you know anything about the status of induction therapy in these patients, whether the frailness that was measured was in part due to the induction therapy and how that might affect the results of your paper?

DR HODARI: That is a very interesting point, but unfortunately that information is not available in NSQIP, so I don’t know which patients had neoadjuvant treatment.

DR SHEN: Bryan, sometimes the medical or the radiation oncologist will balk at giving these patients induction therapy because they think they’re too frail. What do you do with those patients then? Some surgeons will offer surgery upfront even for a T3 or N1 tumor if they or their oncology colleagues don’t think the patient can tolerate induction. What do you do?

DR MEYERS: Well, I think generally we offer them, with the induction followed by surgery, we’re offering them the least morbid or least impactful therapy first. And so if they’re an oncologist you work with regularly and they’re reluctant to give them chemoradiation, then I’d be pretty reluctant to give them surgery. I would think maybe that patient might get radiation alone or you start thinking about palliative strategies if they won’t even consider giving them chemoradiation.

But if they’re objecting to the overall strategy, you know, sometimes we’ve run into patients where you think this patient is either surgery or chemoradiation but they’re not both, then it sort of depends on the detailed discussion with the patient and their family. If they have nodal disease, then offering them surgery alone seems like it’s inappropriate therapy.

DR JUAN ESCALON (Hartford, CT): I just had a quick comment or question with regard to the factors that you said were the independent risk factors for this operation. You mentioned prealbumin, and it’s been quoted in multiple other studies that nutritional status is certainly an independent risk factor for morbidity and mortality in this operation. What are your thoughts on that?

DR HODARI: Yes, in other studies it has been shown to be an independent risk factor, but in our data it wasn’t statistically significant. It would be interesting to look at the STS data, which is another large database, and see if it is an independent risk factor.

DR LERUT: It’s not a question, if I may, it’s just a comment. What I’m hearing here again, and we are confronted with more and more presentations that are dealing with a search on the database. And at the end of the discussion, usually the conclusions are that they cannot be consolidated because of lack of information out of the databases. So is it not time to revise the database because they are too superficial, as we hear again because there are so many data missing.

DR VARGHESE: I’m just going to clarify, which database are you talking about, the NSQIP database or?

DR LERUT: Not only the NSQIP. I think it’s equally valid for the STS database also. Usually you get too many deficiencies in the database.

DR VARGHESE: I mean, I think it’s an interesting point, but I think it’s beyond the scope of this paper.

DR LERUT: I know.

DR VARGHESE: No problem.