Association between frailty status and complications in patients undergoing surgical excision of malignant esophageal neoplasms

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Abstract

Background Research within the last decade highlights the patients' frailty status as an important predictor of esophageal cancer outcomes, but the literature evaluating frailty's role in these patients remains limited. We evaluated the role of frailty in patients undergoing resection of malignant esophageal neoplasms.

Methods We used the Nationwide Readmissions Database from 2016 and 2017 to identify patients who underwent excision of a malignant esophageal neoplasm. Patient frailty was queried using the Johns Hopkins Adjusted Clinical Groups frailty-defining diagnosis indicator. Propensity score matching identified 289 frail patients and 281 non-frail patients. Mann-Whitney *U* testing was performed and receiver operating characteristic (ROC) curves were created, following the creation of logistic regression models for predicting discharge disposition. The area under the curve (AUC) served as a proxy for model performance.

Results Frail patients had significantly more nonroutine discharges, longer inpatient lengths of stay, higher costs, more acute infections, posthemorrhagic anemia and deep vein thrombosis, and greater mortality ($P<0.05$). No significant differences were found between the 2 cohorts with respect to readmission rates, pulmonary embolism or dysphagia. Predictive models for patient discharge disposition demonstrated that frailty status in combination with age resulted in better ROC curves (AUC: 0.652) compared to models using age alone (AUC: 0.601).

Conclusions Frailty was found to be significantly correlated with higher rates of inpatient medical complications following esophagectomy. The inclusion of patient frailty status in predictive models for discharge disposition resulted in a better predictive capacity compared to those using age alone.

Keywords Esophagus, malignancy, frailty, oncology, gastrointestinal

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Introduction

Esophageal cancer is the seventh most common type of newly diagnosed cancer worldwide, with over 600,000 cases in 2020 [1]. While squamous-cell carcinoma remains the most predominant esophageal cancer worldwide, because of the high level of tobacco and alcohol abuse [2,3], rates of esophageal adenocarcinoma are rapidly increasing in the United States in parallel with the increasing rates of obesity [3-5]. Overall, esophageal cancer accounts for 3.1% of all new cancers and 5.5% of all cancer deaths, representing 1 of every 18 cancer deaths annually [1]. This high mortality can be explained by the fact that esophageal cancer usually presents clinically at later stages, with only 18% of cancers still confined to the primary site at diagnosis [6]. Recent advances in curative intent therapy include the adoption of trimodality therapy (carboplatin, paclitaxel and radiotherapy, followed by surgery) for early-stage disease, as examined in the CROSS trial, and neoadjuvant treatment with nivolumab after surgical resection, as seen in the ChckMate577 trial, which have demonstrated improved survival rates [7,8]. Additional advances in chemotherapy for esophageal cancer include the FLOT regimen, which consists of docetaxel, oxaliplatin, leucovorin, and 5-fluorouracil. The ESPOPEC trial investigated the efficacy of neoadjuvant chemoradiation with the CROSS protocol [9]. Perioperative chemotherapy has resulted in better 5-year survival compared with surgery alone. Despite these advances, the prognosis remains poor, with an overall 5-year post-esophagectomy survival rate of around 20% (range 5-47%), with the longest survival seen among those diagnosed at earlier stages [4,5,10].

Frailty is defined as a clinically recognizable state of increased vulnerability resulting from age-associated physiological decline, leading to homeostatic imbalance [11]. It has been operationally defined by Fried *et al* as meeting 3 of the following 5 phenotypic criteria: low grip strength, low energy, slowed walking speed, low physical activity, and/or unintentional weight loss [11-13]. Frail patients continue to be at higher risk of poor health outcomes, including falls, disability, perioperative complications, readmissions and death. Frailty has been shown to be a more accurate predictor of outcomes than age and other patient demographics, especially in patients undergoing complex surgeries [14], as well as being a robust predictor of outcomes in patients who undergo cardiac surgery or cranial neurosurgery [15-18].

As contemporary literature suggests that frailty may be a better predictor of complications than age and other patient demographics, our study aimed to investigate the role of frailty in predicting postoperative outcomes in patients undergoing esophageal excision for malignant esophageal carcinoma. We hypothesized that frail patients would have higher rates of postoperative complications, higher rates of medical complications, and a more complicated hospital course overall, compared to non-frail patients. In addition, using predictive analytics and modeling, we aimed to demonstrate an improved performance of statistical models in predicting patient discharge disposition when frailty status was taken into account. Such an understanding would aid physicians in the appropriate management of patients with newly diagnosed esophageal cancer.

Materials and methods

Data source

In this study, we used the 2016 and 2017 Healthcare Cost and Utilization Project (HCUP) Nationwide Readmissions Database (NRD). The NRD is a large yearly database that contains national information regarding inpatient demographics, diagnoses, procedures and readmissions. Each year of the NRD can be purchased from the HCUP website and is designed to facilitate nationally-representative inpatient and readmission analysis when the appropriate NRD discharge weights are applied. Hospital admissions are de-identified and are represented as unique patient linkages to allow for accurate patient tracking throughout the calendar year. Patient diagnoses and procedures of interest for this study were queried using the International Classification of Diseases, Tenth Revision (ICD-10) codes, and cost-to-charge ratios, which are imputed from national hospital-specific or hospital group-averaged all-payer inpatient cost data, and may be utilized to convert total hospital charges to all-payer inpatient costs. Institutional Review Board approval was not necessary, as this study utilized a publicly available de-identified dataset.

Patient sample

Between 2016 and 2017, we identified a total of 78,689 inpatient admissions with ICD-10 codes for malignant esophageal neoplasm (ICD-10: C15.x). Within this cohort, appropriate coding (ICD-10: 0DB5xZZ) was used to identify 1159 patients (1.5%) who underwent esophageal resection for a malignant esophageal neoplasm (Fig. 1). Frail patients were identified using the Johns Hopkins Adjusted Clinical Groups (JHACG) frailty-defining diagnosis indicator, which uses 10 categories of ICD-10 codes (malnutrition, dementia, vision impairment, decubitus ulcer, urine control, weight loss, fecal control, social support, difficulty walking, and history of a fall) to predict a patient's frailty status [19]. Several studies have confirmed the clinical validity of the JHACG frailty-defining diagnosis indicator [19-22].

The cohort was then subdivided into frail (n=289) and propensity score-matched non-frail (n=281) patients. Nearest-neighbor propensity score matching for age, sex, insurance type, median income by ZIP code, and NRD discharge weighting was performed using the R "MatchIt" algorithm [23]. In this technique, parametric models are chosen based on the minimum "distance" parameter, which is determined through logistic regression models that minimize the propensity score with no replacement. MatchIt improves parametric statistical models and reduces model dependence by preprocessing data with semi-parametric and non-parametric matching methods. Model balance, defined as the similarity of empirical covariate distributions between the 2 groups undergoing propensity matching, is analyzed and the model with the best balance is selected to ensure best model fit (Fig. 2). Complications queried for analysis in this study included postoperative infections, acute posthemorrhagic anemia, dysphagia, mortality, readmission rates, urinary tract infection (UTI), pulmonary embolism (PE), deep vein thrombosis (DVT), inpatient length of stay (LOS), costs, and discharge disposition. Nonroutine discharges were defined as discharges to places other than home (e.g., skilled nursing facility [SNF], home health care [HHC], short-term care facility, etc.).

Statistical analysis

All statistical analysis was conducted in RStudio (Version 1.3.959). Following propensity score matching, chi-square tests were performed to evaluate differences between categorical variables. Mann-Whitney *U* testing was performed to evaluate statistically significant differences in continuous data. Binarized patient complication variables were analyzed in terms of odds ratios using the "Epitools" package, and *post hoc* receiver

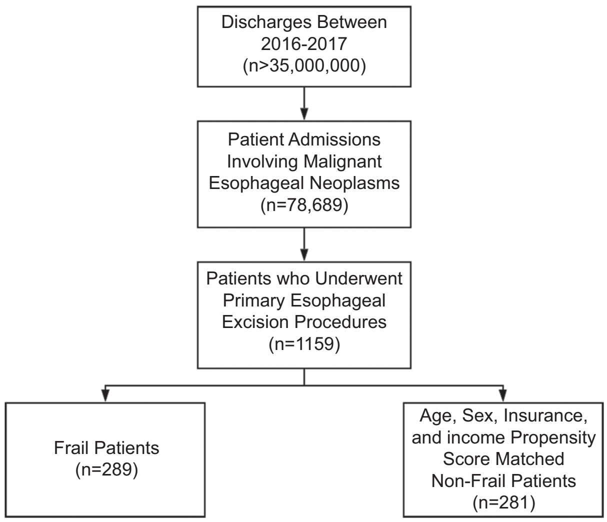

Figure 1 Patient selection flowchart for this study

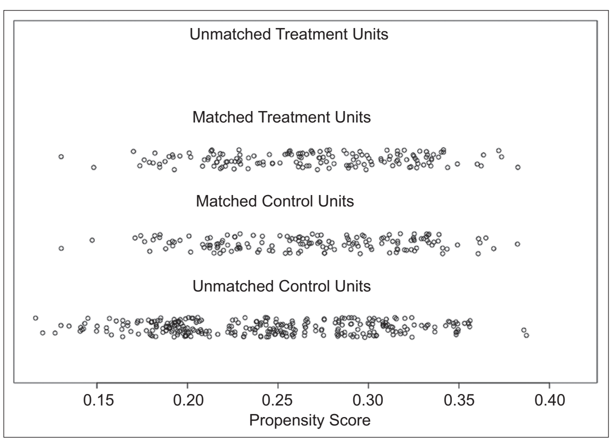

Figure 2 Distribution of propensity scores following matching. Frail patients are shown as Matched Treatment Units and propensity matched non-frail patients are shown as the Matched Control Units. The Unmatched Control Units represent non-frail patients who were not chosen by the propensity matching algorithm. The comparable distribution of patients in both matched treatment and control units implies that excellent propensity score matching was achieved

operating characteristic (ROC) curves were implemented following the creation of logistic regression models for relevant postoperative complications, with both age and frailty status as predictor variables. The area under the curve (AUC) of each ROC was computed and served as a proxy for model performance. All statistical tests were 2-sided with P<0.05 defined as significant.

Results

Demographics

The average age of the frail cohort was 65.0±9.3 years and 19.8% were female. The average age of the non-frail cohort was 64.9±9.5 years and 17.5% were female. As the 2 cohorts were propensity score matched, comparisons of age, sex, insurance type and median income quartile by ZIP code between the 2 cohorts found no statistically significant differences. No significant differences were found between hospital size (P=0.46) and teaching status (P=0.42) in the 2 cohorts. However, significant differences were found between frail and non-frail patients when discharge dispositions were compared (P=0.0020) (Table 1).

Predictive models and ROC analysis

Two sets of logistic regression models were developed: the first used age alone as the primary predictor, while the second used patient frailty status and age. These models were tested to evaluate their prediction of patient discharge status, which was found to be significant. ROCs were plotted for both the logistic regression models (Fig. 3). As seen in Fig. 3, the logistic regression models using frailty and age as the primary predictors outperformed the model using age alone.

Postoperative complication rates

During the primary admission, the costs associated with inpatient stay were significantly higher for frail patients compared to non-frail patients (frail: $81,994.34±$72,418.47 vs. non-frail: $47,269.95±$31,512.09, P<0.001). Similarly, frail patients had a significantly longer inpatient LOS compared to non-frail patients (frail: 20.0±15.7 days vs. non-frail: 11.7±9.2 days, P<0.001).

Complication rates were found to be significantly higher in frail patients compared to non-frail patients. More specifically, frail patients had higher rates of postoperative infection (P=0.0020), acute posthemorrhagic anemia (P<0.001), pneumonia (P=0.0079), UTI (P=0.029), DVT (P<0.001), and mortality (P=0.014) (Table 2). However, rates of PE (P=0.10), dysphagia (P=0.14), and readmission (P=0.72) did not differ significantly between the 2 cohorts.

Discussion

In this 2-year retrospective cohort analysis, we evaluated the impact of frailty on postoperative complications in patients undergoing esophagectomy for a malignant esophageal neoplasm. By comparing a cohort of frail geriatric patients to a propensity-matched cohort of non-frail geriatric patients, we found that frail patients were associated with higher rates of medical complications immediately after surgery, including higher rates of postoperative infections, acute posthemorrhagic anemia, pneumonia, UTI, DVT, and mortality. However, no significant differences were found between frail and non-frail patients with regard to PEs, dysphagia, or readmission rates. The higher complication rates probably explain the longer LOS

Table 1 Demographics of frail and non-frail patients

Demographics	Frail patients (n=289)	Propensity matched non-frail patients (n=281)	P-value
Age (years)	65.0±9.3	64.9±9.5	0.66
Sex			
Female, n (%)	57 (19.8%)	49 (17.5%)	0.67
Male, n (%)	232 (80.2%)	232 (82.5%)	
Insurance			
Medicare, n (%)	159 (55.0%)	148 (52.7%)	0.84
Medicaid, n (%)	32 (11.1%)	18 (6.4%)	
Private, n (%)	90 (31.1%)	110 (39.1%)	
Other, n (%)	8 (2.8%)	5 (1.8%)	
Median income by zip code			
Quartile 1, n (%)	80 (27.7%)	73 (26.0%)	0.89
Quartile 2, n (%)	72 (24.9%)	77 (27.4%)	
Quartile 3, n (%)	87 (30.1%)	65 (23.1%)	
Quartile 4, n (%)	50 (17.3%)	66 (23.5%)	
Hospital type			
Metropolitan non-teaching, n (%)	23 (8.0%)	17 (6.0%)	0.42
Metropolitan teaching, n (%)	267 (92.0%)	263 (93.6%)	
Non-metropolitan, n (%)	0 (0.0%)	1 (0.4%)	
Discharge Disposition			
Routine, n (%)	60 (20.8%)	106 (37.7%)	0.0020
Nonroutine, n (%)	229 (79.2%)	175 (62.3%)	

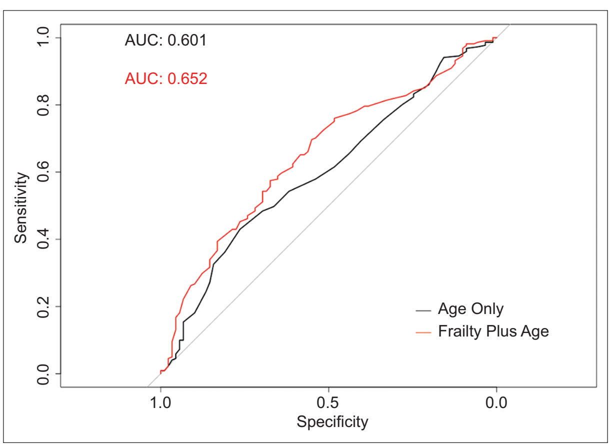

Figure 3 ROC plot for prediction of nonroutine discharge status. The black ROC represents the logistic model using age alone as the primary predictor, and the red ROC represents the logistic model using frailty status and age as the primary predictors. A noticeable increase in predictive power occurs when frailty is jointly considered for prediction of discharge status
ROC, receiver operating characteristic curve; AUC area under the curve

and higher hospital costs associated with frailty. Predictive models evaluated by ROC curves also demonstrated improved model performance with the addition of frailty when predicting discharge disposition, allowing for more accurate patient risk triage and hospital resource utilization.

Over the past decade, frailty has been more popularly utilized for assessing rates of morbidity, mortality and postoperative outcomes in the field of gastroenterology, with evidence pointing towards the importance of assessing frailty in preoperative risk-stratifying assessments [24-26]. Hodari *et al* previously elucidated the relationship between patient frailty and morbidity and mortality in patients undergoing esophagectomy procedures [27]. Their focus was placed on evaluating a 5-point modified frailty index (mFI) in patients who undergo esophagectomy procedures, and their study demonstrated that frailty scores of 0, 1, 2, 3, 4 and 5 had associated morbidity rates of 17.9%, 25.1%, 31.4%, 34.4%, 44.4% and 61.5%, respectively [27]. Esophagectomy has historically been associated with higher levels of morbidity and mortality, and as a result surgical management has shifted towards multidisciplinary care to improve short-term outcomes. Perioperative treatment protocols, such as enhanced recovery after surgery (ERAS) programs, have been implemented in various surgical disciplines and have been shown to decrease LOS, postoperative complications, and postoperative morbidity. However, the use of these protocols in esophageal surgery is still limited. Components of the ERAS protocol for esophageal cancer included proper preoperative nutritional support, using minimally invasive surgical techniques, and avoiding routine postoperative nasogastric tube insertion, abdominal draining, and Foley catheter insertion.

Our study supports the finding of Hodari *et al*, that frail patients have overall higher rates of morbidity compared to non-frail patients. The JHACG frailty index is a binary classification system formulated to capture multiple domains of frailty (i.e., functional, cognitive, psychological and socioeconomic), and it has been shown to identify patients who have limitations in their activities of daily living [19,28]. Whereas the mFI is useful in establishing degrees of morbidities as frailty becomes more severe, the JHACG frailty index is a superior tool when it comes to comparing frail patients to non-frail counterparts.

Table 2 Management and complications in frail and non-frail patients

Parameters	Frail patients (n=289)	Propensity matched non-frail patients (n=281)	P-value
Mean all-payer cost	$81,994.34±$72,418.47	$47,269.95±$31,512.09	<0.001
Mean LOS (days)	20.0±15.7	11.7±9.2	<0.001
Infection	76 (26.3%)	24 (8.5%)	0.0020
Acute posthemorrhagic anemia	112 (38.8%)	40 (14.2%)	<0.001
Pneumonia	60 (20.8%)	20 (7.1%)	0.0079
UTI	17 (5.9%)	5 (1.8%)	0.029
DVT	24 (8.3%)	1 (0.4%)	<0.001
PE	9 (3.1%)	1 (0.4%)	0.10
Dysphagia	78 (27.0%)	51 (18.1%)	0.14
Mortality	38 (13.1%)	11 (3.9%)	0.014
Readmission	100 (34.6%)	88 (31.3%)	0.72

LOS, length of hospital stay; UTI, urinary tract infection; DVT, deep vein thrombosis; PE, pulmonary embolism

For instance, a systematic review by Ornaghi *et al* of patients undergoing radical cystectomy (RC) for bladder cancer found that, though the mFI tends to be the most commonly used frail index in that field, the JHACG index was the best predictor of early postoperative RC-related adverse outcomes [29]. In addition, our study implemented propensity score matching and robust predictive models to improve current paradigms of risk stratification and prediction of postoperative complications. Our data reinforce previous evidence in the field of gastroenterology and gastrointestinal surgery, though utilizing a better predictor of adverse outcomes, and demonstrate the predictive validity of frailty in patients with gastrointestinal malignancies.

Historically, gastrointestinal surgical risk analysis has relied on patient demographics alone, primarily placing a large onus on age as a predictor for complications [30,31]. Through the creation of robust predictive models, it was possible to quantify the predictive value of patient frailty status in predicting patient discharge disposition. Specifically, the addition of frailty to our predictive models using age to predict nonroutine patient discharges increased the AUC from 0.601 to 0.652. In general, an AUC of 0.50 demonstrates a random guess and AUC values greater than 0.70 are defined as strongly predictive [32]. While neither model quite achieves 0.70, the addition of frailty increased the AUC and the predictive capabilities of our model significantly. Previous studies have shown that the addition of frailty to the American Society of Anesthesiologists, Lee's revised cardiac risk, and Eagle indices may improve the overall performance of predictive models in a heterogeneous cohort of elderly patients undergoing surgery [14,24]. However, this association has not yet been established in patients undergoing esophageal surgery for malignant neoplasms, and our study is the first to show that frailty improves the prediction of outcomes in this specific population of patients. Future work should focus on identifying additional variables that may be used to supplement models incorporating frailty, to boost the AUC past 0.70.

The findings of this study also provide an opportunity to improve the inpatient management of patients who undergo surgery for esophageal neoplasms. Using increasingly robust and predictive models, it becomes possible to predict potential patient outcomes with high accuracy, allowing for better resource utilization. Previous studies using machine learning models and predictive modeling have successfully identified factors that are correlated with discharge turnaround time and status, allowing for the prediction of discharge status and shorter inpatient LOS [33,34]. This may also be possible for patients admitted for surgical excision of esophageal neoplasms. For example, patients identified as high-risk for nonroutine discharge using our models may be prioritized for consultation with social services, such as physical and occupational therapy, and coordination of placement in SNF, HHC, or short-term hospital facilities. This may potentially save time and resources and expedite transfer to facilities that can provide patients with appropriate care. Furthermore, our study identified specific complications that are more likely to affect frail patients, highlighting increasingly common complications in frail patients, and allowing for more tailored inpatient management.

This study had several limitations. First, it was subject to the limitations of retrospective cohort analyses. Namely, the quality of analysis is dependent on the depth and accuracy of patient encounters documented in the NRD, and Berkson's bias is present when working with inpatient databases. Furthermore, this study is limited by being a retrospective analysis during a narrow time interval (2016 and 2017 only). However, the dates were chosen based on the implementation of mandatory ICD-10 coding in late 2015, which allowed for more detailed codes to be drawn for analysis. In addition, because the database relies on ICD-10 coding, it is not possible to query TNM staging or type of esophagectomy procedure. Lastly, the NRD allows for retrospective readmission analysis within one calendar year (January to December). Therefore, additional readmissions not occurring within the same calendar year are not captured and cannot be analyzed using the NRD.

To conclude, our study suggests that patient frailty status strongly correlates with rates of medical complications, costs, LOS, and discharge disposition in patients who undergo esophagectomy for esophageal cancer. When frailty was incorporated into logistic models, it improved the prediction of patient discharge disposition compared to patient age alone. Overall, frailty represents a robust predictor of patient outcomes, and a better understanding of frailty may aid in medical and surgical decision making when considering patients with esophageal cancer. Further research, including a multicenter analysis with a large number of participants, will be necessary to fully understand the role of frailty in the outcomes of patients with malignant esophageal neoplasms.

Summary Box

What is already known:

- Research has highlighted patient frailty status as an important predictor of outcomes
- Various adjutant chemotherapy agents, combined with surgery, have been shown to improve mortality from esophageal cancer
- Frailty in esophagectomy for esophageal cancer has been shown to be correlated with rates of postoperative morbidity and mortality

What the new findings are:

- Frailty was found to be significantly correlated with medical complications immediately after surgery, including higher rates of postoperative infections, acute posthemorrhagic anemia, pneumonia, urinary tract infections, deep vein thrombosis and mortality in patients undergoing esophagectomy for a malignant esophageal neoplasm
- Inclusion of patient frailty status in predictive models improved their predictive capacity compared to those using age alone
- Predictive modeling allowed for the creation of receiver operating characteristic curves for nonroutine discharge, which demonstrated that the addition of frailty to age alone within predictive models improved the area under the curve significantly

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