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The influence of frailty on perioperative outcomes in patients undergoing surgical resection of liver metastases: a nationwide readmissions database study

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Abstract

Background Liver metastases arise frequently from primary colorectal, pancreatic, and breast cancers. Research has highlighted the patient's frailty status as an important predictor of outcomes, but the literature evaluating the role of frailty in patients with secondary metastatic disease of the liver remains limited. Using predictive analytics, we evaluated the role of frailty in patients who underwent hepatectomy for liver metastases.

Methods We used the Nationwide Readmissions Database from 2016-2017 to identify patients who underwent resection of a secondary malignant neoplasm of the liver. Patient frailty was evaluated using the Johns Hopkins Adjusted Clinical Groups (JHACG) frailty-defining diagnosis indicator. Propensity score matching was performed and Mann-Whitney *U* testing was used to analyze complication rates. Receiver operating characteristic (ROC) curves were created following creation of logistic regression models for predicting discharge disposition.

Results Frail patients reported significantly higher rates of nonroutine discharges, longer inpatient stays, greater costs, higher rates of acute infection, posthemorrhagic anemia, urinary tract infection (UTI), deep vein thrombosis (DVT), wound dehiscence and readmission, and greater mortality ($P<0.05$). Predictive models for patient discharge disposition, DVT and UTI demonstrated that the use of frailty status and age improved the area under the ROC curves significantly compared to models using age alone.

Conclusions Frailty was found to be significantly correlated with higher rates of medical complications during inpatient stay following hepatectomy in patients with liver metastasis. The inclusion of patient frailty status in predictive models improved their predictive capacity compared to those using age alone.

Keywords Liver, metastasis, frailty, oncology, hepatobiliary

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Conflict of Interest: None

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Introduction

Liver metastases are neoplasms that have spread from cancer elsewhere in the body [1], arising most frequently from colorectal, pancreatic, and breast cancers. In fact, 50% of patients with colorectal cancer are diagnosed with liver metastases [2]. The liver is the most common organ affected by metastasis, because of its large blood supply [1,3]. As the incidence of colon cancer continues to rise, it is increasingly important to categorize its association with liver metastases [4]. The median 1-year survival rate of patients with liver metastases (15.1%) is significantly lower than the 1-year survival rate for patients diagnosed with non-hepatic metastases (24.0%). In a

study that reviewed 2.4 million patients diagnosed with any type of cancer, 5.14% presented with liver metastases at the time of initial diagnosis. The most frequent primary cancer sources in this study were the pancreas (35.6%) and colon-rectum (26.9%) [5]. Despite their advanced cancer stage, most of these patients were asymptomatic, with only some reporting constitutional symptoms [1]. In fact, liver metastases are more common than primary liver cancer in the US, with 5-year survival rates ranging around 25% for those not receiving early surgical intervention [6]. The most common treatment of liver metastases remains surgical resection [7], although these cases are frequently inoperable because of the heavy metastatic burden. Even with resection, the prognosis of this disease remains extremely poor, with recurrence of disease in two thirds of patients [7,8].

Frailty is an important factor affecting patients' health outcomes, as it reflects the patients' overall physiological reserve [9]. Frailty is defined as an age-associated condition that reduces the patient's physiologic ability to handle stressors, both chronic and acute [10]. Regarding patients undergoing elective surgery, frailty has been reported to be a more accurate predictor of outcomes than an array of other patient demographics, including age [11]. In fact, frailty has proved to be an independent, more accurate preoperative predictive risk factor, even after adjustment for socioeconomic status, depression, and disability [12].

Because frailty is an important risk factor affecting health outcomes, we aimed to investigate its role in predicting outcomes in patients with liver metastases who underwent surgical resection. We hypothesized that frail patients would have a higher rate of postoperative complications and longer hospital stays. Finally, using statistical modeling and predictive analytics, we investigated the relationship between patient's frailty status and perioperative outcomes. The goals of this study were to help surgeons better identify which patients are metastasectomy candidates, to improve perioperative management for frail patients, and to assist physicians in communicating more accurate prognoses to patients diagnosed with secondary metastatic disease of the liver.

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 an annually updated 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 a nationally-representative analysis of inpatients and readmissions when the appropriate NRD discharge weights are applied. Patient 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 in combination with cost-to-charge ratios. The latter are imputed from national hospital-specific or hospital-group-averaged all-payer inpatient cost data, which may be used to convert total hospital charges to all-payer inpatient costs. Institutional Review Board approval was not necessary as this study was based on a publicly available de-identified dataset.

Patient sample

Between 2016 and 2017, we identified a total of 28,781 inpatient admissions with ICD-10 codes for liver resection procedures (ICD-10: 0FT0xZZ, 0FBxxZZ). Within this cohort, appropriate coding was utilized to identify 10,799 (37.5%) patients who underwent a liver resection procedure for liver metastases. 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 [13]. A patient is deemed categorically frail if at least one of these comorbidities has been discovered. Frailty is measured over 5 phenotypic characteristics, including accidental weight loss, tiredness, poor energy expenditure, limited grip strength and/or sluggish walking pace. This measure, which takes into account the decline in a number of physiological systems, was created to help medical professionals identify people more susceptible to suffering negative health effects [13]. Several studies have confirmed the clinical validity of the JHACG frailty-defining diagnosis indicator [13-16].

Based on the above, the cohort was then subdivided into frail (n=766) and propensity score matched non-frail (n=749) patients. Nearest-neighbor propensity score matching for age, sex, Elixhauser Comorbidity Index (ECI), insurance type, median income by ZIP code, and NRD discharge weighting was performed using the R "MatchIt" algorithm [17]. In this technique, parametric models are chosen based on the minimum "distance" parameter, 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

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selected to ensure the best model fit (Fig. 1). Complications queried for analysis in this study included postoperative infections, acute posthemorrhagic anemia, ileus, wound dehiscence, 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, home health care, short-term care facility, etc.)

Statistical analysis

All statistical analysis was conducted in RStudio (Version 1.3.959). Following propensity score matching, chi-squared tests were performed to evaluate differences between categorical variables. Mann-Whitney *U* test was performed to evaluate statistically significant differences in continuous data. Continuous variables followed a normal distribution and are thus reported as mean ± standard deviation. Binarized patient complication variables were analyzed using the "Epitools" package, with *post hoc* receiver operating characteristic (ROC) curves implemented following the creation of logistic regression models for relevant postoperative complications, using both age and frailty status as predictor variables. ROC curves were constructed for outcomes including nonroutine discharge, DVT and UTI, as these complications showed the greatest improvement in predictive power with the addition of frailty when considered against age alone. The area under the curve (AUC) of each ROC was computed and served as a proxy for model performance. DeLong's test for 2 correlated ROC curves was utilized to compare ROC AUCs. All statistical tests were 2-sided, with P<0.05 defined as significant.

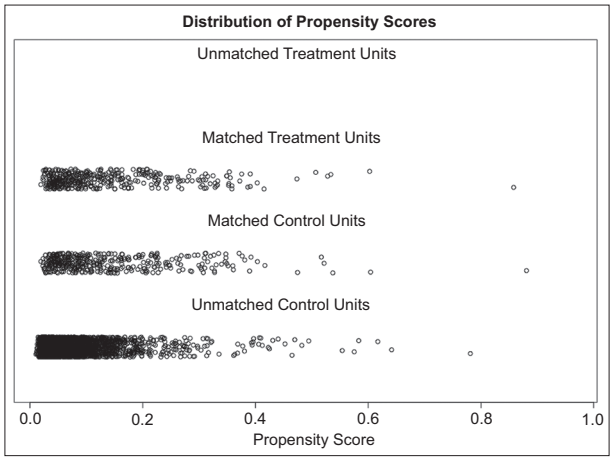

Figure 1 Distribution of propensity scores following matching. Frail patients are shown as Matched Treatment Units and propensity matched non-frail patients are shown as the Matched Control Units. The Unmatched Control Units represent non-frail patients who were not chosen by the propensity matching algorithm. The comparable distribution of patients in both matched treatment and control units implies achievement of excellent propensity score matching

Results

Demographics

The average age of the frail cohort was 61.5±14.2 years and 49.0% were female. The average age of the non-frail cohort was found to be 62.7±13.4 years and 48.6% were female. Because the 2 cohorts were propensity score matched, the age, sex, ECI, insurance type and median income quartile by ZIP code did not differ statistically between the 2 cohorts. No significant differences in hospital size (P=0.63) or teaching status (P=0.66) were found between the 2 cohorts. However, significant differences were found between frail and non-frail patients when comparing discharge disposition (P<0.001) (Table 1).

Predictive models and ROC analysis

Two sets of logistic regression models were developed: the first used age alone as the primary predictor, and the second used patient frailty status and age as the primary predictors. These models were used to assess the predictive capabilities of age and frailty status for nonroutine discharge, DVT and UTI. ROCs were plotted for both the logistic regression models for each outcome (Fig. 2-4). As the figures show, the logistic regression models using frailty and age as primary predictors outperformed the model using age alone. In addition, the AUC of the ROC incorporating frailty was found to be significantly higher when compared to age alone for nonroutine discharge (P=0.017), DVT (P=0.040), and UTI (P=0.040).

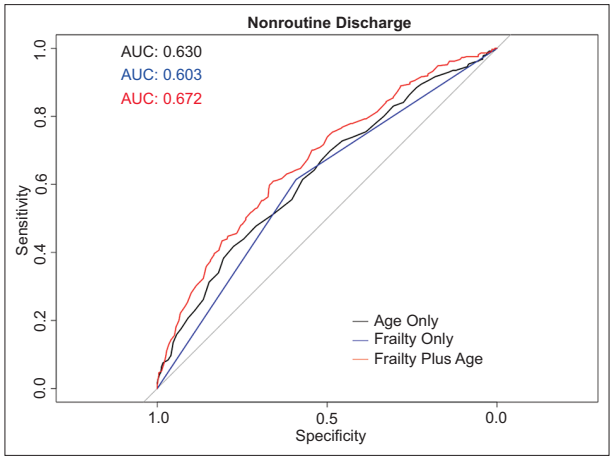

Figure 2 Receiver operating characteristic (ROC) plot for prediction of nonroutine discharge status. The black ROC represents the logistic model using age alone as the primary predictor, the blue ROC represents the logistic model using frailty alone as the primary predictor, and the red ROC represents 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
AUC, area under the curve

Table 1 Demographics of frail and non-frail patients

Characteristics	Frail patients (n=766)	Propensity matched non-frail patients (n=749)	P-value
Age (years)	61.5±14.2	62.7±13.4	0.21
Elixhauser comorbidity index	7.2±3.2	7.1±3.2	0.76
Sex			
Female, n (%)	375 (49.0%)	364 (48.6%)	0.78
Male, n (%)	391 (51.0%)	385 (51.4%)	
Insurance			
Medicare, n (%)	370 (48.3%)	400 (53.4%)	0.68
Medicaid, n (%)	105 (13.7%)	49 (6.5%)	
Private, n (%)	259 (33.8%)	283 (37.8%)	
Other, n (%)	32 (4.2%)	17 (2.3%)	
Median income by zip code			
Quartile 1, n (%)	202 (26.4%)	201 (26.8%)	0.83
Quartile 2, n (%)	186 (24.3%)	181 (24.2%)	
Quartile 3, n (%)	211 (27.5%)	166 (22.2%)	
Quartile 4, n (%)	168 (21.9%)	202 (27.0%)	
Hospital type			
Metropolitan non-teaching, n (%)	57 (7.4%)	67 (8.9%)	0.66
Metropolitan teaching, n (%)	698 (91.1%)	673 (90.0%)	
Non-metropolitan, n (%)	12 (1.5%)	9 (1.1%)	
Discharge disposition			
Routine, n (%)	350 (45.7%)	489 (65.3%)	<0.001
Nonroutine, n (%)	416 (54.3%)	260 (34.7%)	

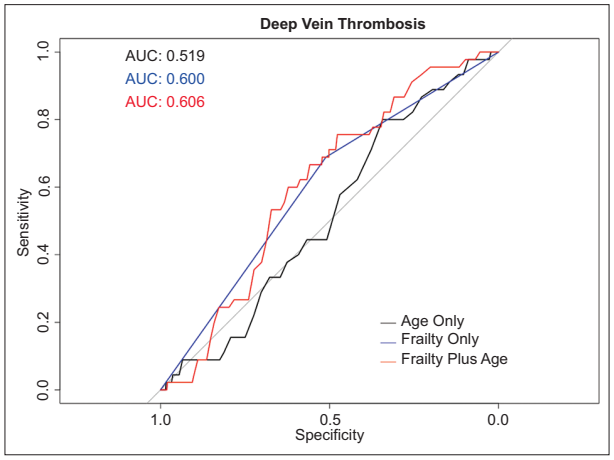

Figure 3 Receiver operating characteristic (ROC) plot for prediction of postoperative deep vein thrombosis (DVT). The black ROC represents the logistic model using age alone as the primary predictor, the blue ROC represents the logistic model using frailty alone as the primary predictor, and the red 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 DVT
AUC, area under the curve

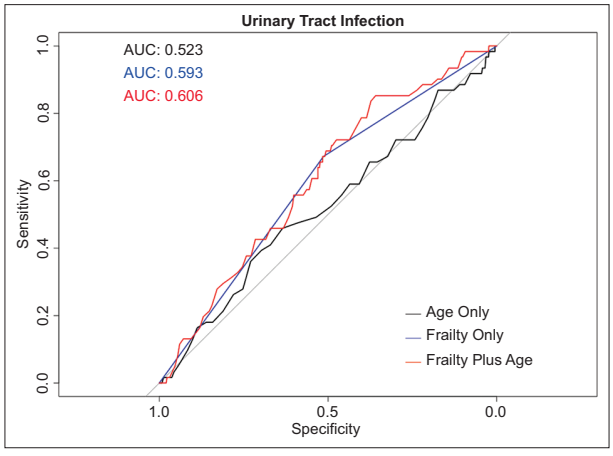

Figure 4 Receiver operating characteristic (ROC) plot for prediction of postoperative urinary tract infection (UTI). The black ROC represents the logistic model using age alone as the primary predictor, the blue ROC represents the logistic model using frailty alone as the primary predictor, and the red 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 UTI
AUC, area under the curve

Postoperative complication rates

During the primary admission, the costs associated with the inpatient stay were significantly higher for frail patients compared to non-frail patients (Frail: $63,164.99±$102,884.00 vs. Non-Frail: $37,103.88±$31,366.27; P<0.001). Similarly, frail patients had a significantly greater inpatient LOS compared to non-frail patients, despite propensity score matching for demographics (Frail: 16.5.0±22.7 days vs. Non-Frail: 8.3±7.2 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<0.001), acute posthemorrhagic anemia (P<0.001), UTI (P=0.0053), DVT (P=0.0093), wound dehiscence (P=0.0026), mortality (P=0.0076), and readmission (P=0.0057) (Table 2). However, rates of pneumonia (P=0.25), PE (P>0.99), and ileus (P=0.58) were not significantly different between the 2 cohorts.

Discussion

In this retrospective study of patients treated surgically for secondary metastatic disease of the liver in 2016 and 2017, we investigated the influence of frailty on perioperative complications. Using propensity score matching techniques, we analyzed the association between frailty and complications of interest, while controlling for demographic confounders. Further modeling allowed for the creation of several ROCs for nonroutine discharge, DVT and UTI, which demonstrated that the addition of frailty to age alone within predictive models improved the AUC significantly. This study contributes to the body of work dedicated to improving the postoperative management of patients who undergo surgical intervention for metastasis to the liver, highlighting specific complications that may predominate in frail populations.

Over the last several decades, frailty has become a topic of particular interest in hepatobiliary surgery, and has been shown to be highly correlated with rates of postoperative morbidity and mortality [18-20]. A 2018 review by Laube *et al* concluded that frailty may affect 17-43% of patients with advanced liver disease: frail patients who undergo hepatectomy have a higher incidence of postoperative complications, with a longer LOS and greater short- and long-term mortality [18,21-24]. In addition, 2 recent 2020 and 2021 studies by Yamada *et al* demonstrated that elderly frail patients undergoing surgery for hepatocellular carcinoma (HCC) had significantly worse overall and disease-free survival compared to non-frail patients [19,20]. These findings suggest that, even when controlling for age, elderly patients who meet clinical criteria for frailty continue to have worse perioperative outcomes. In other words, the decreased physiological reserve that defines frailty is poorly captured by age alone; thus, considering age together with patient frailty status may provide a superior predictor of perioperative morbidity.

Furthermore, while frailty has been well studied within the field of hepatobiliary surgery, data outlining the influence of frailty in patients with metastatic disease to the liver are still limited. A 2021 study by Tokuda *et al* used multivariate regression analysis to assess the role of frailty in 29 frail and 58 non-frail patients with primary colorectal cancer (CRC) metastatic to the liver [25]. Their study found that overall and disease-specific survival rates were significantly worse in frail patients, while 21 of 58 patients with disease recurrence were frail patients, representing 72.4% of the frail cohort [25]. Similar findings were also demonstrated in a 2021 study by Dauch *et al*, who used the modified frailty index and multivariable regression analysis to evaluate the influence of frailty on postoperative outcomes in patients with primary CRC metastatic to the liver [26]. In their study, they found that frail patients had significantly higher rates of minor/major complications, readmissions, unfavorable discharges and mortality, and a longer LOS [26]. While both of these studies contribute important information to the existing literature, our study expands upon these studies in several important ways. First, we used propensity score matching techniques, which have been shown to be more robust in estimating causal effects using observational data compared to multivariate and multivariable analyses [27]. Additionally, our study included all patients with secondary metastatic disease

Table 2 Complications in frail and non-frail patients

Complications	Frail patients (n=766)	Propensity matched non-frail patients (n=749)	P-value
Mean all-payer cost	$63,164.99±$102,884.00	$37,103.88±$31,366.27	<0.001
Mean LOS (days)	16.5±22.7	8.3±7.2	<0.001
Infection	144 (18.8%)	48 (6.4%)	<0.001
Acute posthemorrhagic anemia	216 (28.2%)	163 (21.8%)	<0.001
Pneumonia	62 (8.1%)	38 (5.1%)	0.25
UTI	79 (10.3%)	39 (5.2%)	0.0053
DVT	54 (7.0%)	22 (2.9%)	0.0093
PE	23 (3.0%)	23 (3.1%)	>0.99
Ileus	103 (13.4%)	70 (9.3%)	0.58
Wound dehiscence	30 (3.9%)	8 (1.1%)	0.0026
Mortality	52 (6.8%)	19 (2.5%)	0.0076
Readmission	390 (50.9%)	308 (41.1%)	0.0057

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

to the liver captured in the NRD, allowing our models to be applicable to all patients with liver metastasis, regardless of the primary origin of the cancer.

Because frailty is undeniably associated with worse outcomes, several studies have investigated interventions that may reduce frailty burden and improve frail patients' outcomes. Frailty is associated with a reduced physiologic reserve and resistance to stressors, resulting in vulnerability to adverse outcomes [18,28]. Intuitively, approaches that increase physiological reserve could act as a means of combating frailty. In a 2021 propensity score-matched study by Tsuchihashi *et al*, patients were started on an exercise regimen the day after HCC resection, and received interventions in the form of physical therapy 5 days per week, ranging through stretching, resistance, balance and aerobic exercises [29]. They found that the patients who completed an in-hospital exercise regimen improved their frailty status and had lower rates of postoperative complications [29]. This study suggests that specific in-hospital interventions may prevent the development of frailty-associated illnesses following surgical intervention for liver cancer. However, they are limited by patient compliance and additional studies are necessary to demonstrate the same findings in patients with secondary metastatic disease of the liver. In addition, a broad body of literature has evaluated the influence of nutrition on frailty. Specifically, adequate energy intake, especially protein intake, has been shown to reduce rates of frailty in large population studies and systematic reviews [30,31]. Thus, a combination of adequate preoperative nutrition and postoperative physical therapy may reduce rates of patient frailty, leading to lower perioperative complication rates in patients like those in our cohort.

This study has several limitations, including those inherent in 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 its retrospective nature, focusing on a narrow range of time (2016 and 2017 only). However, the choice of dates was due to the implementation of mandatory ICD-10 coding in late 2015, which allowed for more detailed codes to be drawn for analysis. 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.

Our study suggests that patient frailty status strongly correlates with rates of medical complications, costs, LOS and discharge disposition in patients with secondary metastatic disease of the liver following surgical intervention. Frailty also improved the prediction of nonroutine patient discharges, DVT and UTI, compared to patient age alone, when incorporated into logistic models. Overall, frailty represents a robust predictor of patient outcomes and a better understanding of frailty may aid surgeons' decision-making following surgical intervention for liver metastases. Further research, including multicenter analyses with a large number of participants, is necessary to fully understand the influence of frailty on outcomes in patients with secondary metastatic disease of the liver.

Summary Box

What is already known:

- Research has highlighted patient frailty status as an important predictor of outcomes
- A variety of therapeutic agents have been evaluated to prevent postoperative recurrence endoscopically and clinically, and to induce and maintain remission
- Frailty is a more accurate preoperative predictive risk factor, even after adjusting for socioeconomic status, depression, and disability
- Frailty in hepatobiliary surgery 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 higher rates of medical complications during inpatient stay following hepatectomy in patients with liver metastasis
- 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 several receiver operating characteristic curves for nonroutine discharge, deep vein thrombosis and urinary tract infection, which demonstrated that the addition of frailty to age alone within predictive models improved the area under the curve significantly

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