

Research Report

Predictive value of 5-Factor modified frailty index in Oncologic and benign hysterectomies

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ABSTRACT

Background: The 5-factor modified frailty index (mFI-5) has been validated against the original 11-factor modified frailty index in gynecologic surgery, however its utility has not been evaluated between benign versus gynecologic oncology patient populations.

Objective: To evaluate the predictive value of the mFI-5 in identifying women at increased risk for major post-operative complications, readmission, or death within 30 days of hysterectomy for benign and oncologic indications.

Methods: Patients who underwent hysterectomy between 2015 and 2017 were identified from the NSQIP database and stratified into benign or malignant indications. Demographic and mFI-5 variables were extracted. The mFI-5 was calculated by dividing the sum of all affirmative variables by the total number of input variables in the database. Logistic regression modeling was performed adjusting for confounders. C-statistic with 95% CI was obtained post-regression.

Results: 80,293 hysterectomies (59,078 benign and 21,215 oncologic) were identified. The benign group was more likely to have an mFI-5 score of 0 (70% vs 50%, $p = 0.001$) and had shorter operative times ($p = 0.001$). In the benign group, mFI-5 was a strong predictor of mortality ($c = 0.819$, CI 0.704–0.933). Within the oncology group, the mFI-5 was a strong predictor of mortality ($c = 0.801$, CI 0.750–0.851), particularly for uterine and cervical cancers. It was moderately predictive of readmission ($c = 0.671$, CI 0.656–0.686) and strongly predictive of Clavien-Dindo class III and IV complications ($c = 0.732$, CI 0.713–0.750).

Conclusion: The mFI-5 is a strong predictor of 30-day mortality and serious postoperative complications. These findings have the potential to improve identification of high-risk patients in the preoperative setting.

1. Introduction

The link between frailty and perioperative morbidity and mortality has been retrospectively established in gynecologic surgery. (Uppal et al., 2015; George et al., 2016; Suskind et al., 2017; Wilkes et al., 2019; Erikson et al., 2011; Mullen et al., 2020; Sia et al., 2020) As a result, optimizing preoperative identification of frail patients is an area of ongoing interest and research, resulting in many frailty indices and scoring systems. (Mullen et al., 2020; Sia et al., 2020; Courtney-Brooks et al., 2012; Orlandini et al., 2020; Kumar et al., 2017; Driver and

Viswanathan, 2017) The modified frailty index (mFI-11) is an 11-factor index developed using the American College of Surgeons' National Surgical Quality Improvement Program (NSQIP) database that has been shown to reflect a patient's frailty as well as to predict the likelihood of postoperative mortality and morbidity across multiple surgical specialties, including gynecology and gynecologic oncology. (Velanovich et al., 2013) Furthermore, a recent systematic review of six frailty identification tools in patients undergoing gynecologic cancer surgery found that mFI-11 was the most utilized and feasible tool. (Di Donato et al., 2021) However, certain variables necessary for the calculation of

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the mFI-11 have been removed from the NSQIP database. As of 2015, only 5 variables of the original 11 remain, forming the basis of the new 5-factor modified frailty index (mFI-5).

A 2018 study comparing the mFI-11 and mFI-5 in terms of ability to predict mortality, postoperative complication, and unplanned 30-day readmission found the two indices were equally predictive across multiple surgical subspecialties. (Subramaniam et al., 2018 Feb) However, while the mFI-5 has been studied further within other surgical specialties, there are only two studies to date looking at the mFI-5 in gynecologic surgery, one of which only included patients undergoing laparotomy. (Dindo et al., 2004; Clavien et al., 2009 Aug) Furthermore, while these two studies included oncologic patients, there are no studies to date evaluating the utility of mFI-5 in differentiating between gynecologic oncology surgery and benign gynecologic surgery populations, a potentially important distinction given the tendency of gynecologic oncology patients to have more comorbidities. (Buckingham et al., 2020) This study therefore aimed to evaluate the predictive value of the new mFI-5 in identifying women at increased risk of postoperative complications, readmission, or death within 30 days of hysterectomy for benign and oncologic indications.

2. Methods

A retrospective cohort study was performed. The American College of Surgeons' NSQIP database was used to identify all women who underwent hysterectomy from January 2015 to December 2017. The NSQIP database is a risk-adjusted database that includes preoperative, surgical procedure, and postoperative data through 30-days postoperatively from 689 hospitals across the United States and worldwide. All data are de-identified and available for research purposes. Data are collected by trained Surgical Clinical Reviewers, entered in a HIPAA-compliant secure platform, and are audited by the American College of Surgeons to ensure reliability. Penn Medicine deemed this study exempt from Institutional Board Review.

Patients were identified as outlined in Fig. 1. Inclusion criteria was having a hysterectomy performed between 2015 and 2017. Performance of a hysterectomy was identified by Current Procedural Terminology (CPT) codes. Patients were stratified into benign or malignant groups by

postoperative diagnosis as determined by International Classification of Diseases, 9th and 10th revision codes. The oncology group was further stratified by cancer type into the following subgroups: ovarian (including primary peritoneal), uterine, cervical, and other. The "other" cancer group included all other gynecologic malignancies (gestational trophoblastic neoplasia, vulvar cancer, and vaginal cancer) as well as malignancies that were non-gynecologic in primary origin but required hysterectomy as part of treatment. Exclusion criteria were a procedure date prior to 2015. Patients who underwent procedures in addition to hysterectomy as indicated by additional CPT codes associated with their procedures were recorded as having had concomitant procedures. These CPT codes were then reviewed and those meeting criteria of involving a major GI, genitourinary, urogynecologic or other abdominal/vulvar procedure were grouped into a category of "major concomitant procedure" for the purpose of analysis. Major procedures included removal of organs, debridements, lysis of adhesions, and other procedures requiring complex surgical skill. Diagnostic scopes (including cystoscopy, colonoscopy, etc) or biopsies were not included in this category.

The mFI-5 is comprised of five variables: hypertension requiring medication, partially-dependent or dependent functional status, insulin-dependent diabetes, COPD, and congestive heart failure. These variables were extracted from the database along as either affirmative or absent for each patient. In accordance with previous literature, the mFI-5 score was calculated by dividing the sum of all affirmative variables by the total number of input variables in the database, with a higher mFI-5 score indicating a higher degree of frailty. (Subramaniam et al., 2018) Twenty-two patients had scores calculated based on 4 variables instead of 5 as they were missing data on one of the variables. In the primary analysis, the mFI-5 was treated as a continuous variable. However, to try and delineate a clinically useful cutoff at or above which patients are considered frail, we additionally performed a secondary analysis to assess the predictive performance of the mFI-5 at cutoff points of 0.4 and 0.6.

The primary outcome was 30-day postoperative mortality. Secondary outcomes included readmission and major postoperative complications within 30 days of surgery. Major complications included septic shock, cardiac arrest, unplanned reintubation, reoperation, surgical site infection, wound dehiscence, vaginal cuff dehiscence, pneumonia,

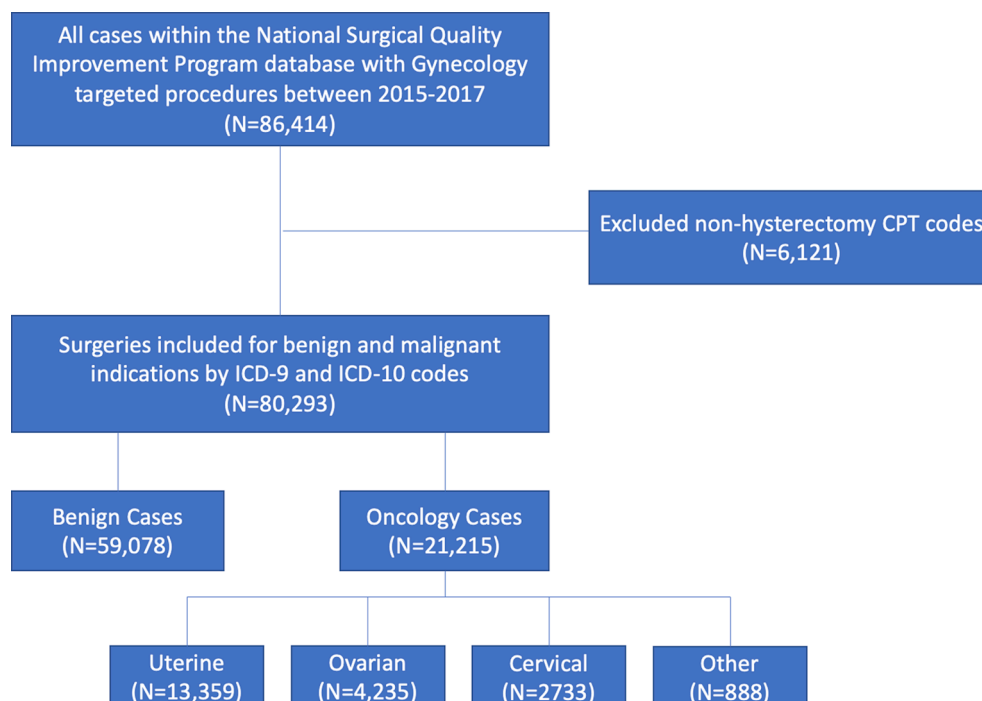


Fig. 1. Benign and oncologic hysterectomies included from the American College of Surgeons' NSQIP database.

pulmonary embolism, deep venous thrombosis, urinary tract infection, transfusion, myocardial infarction, acute renal failure, and cerebrovascular accident. These outcomes were chosen based on those described in previous literature. (Subramaniam et al., 2018) As a sensitivity analysis within the oncology cohort, the outcomes were classified according to the Clavien-Dindo system. (Dindo et al., 2004; Clavien et al., 2009) The mFI-5 was then evaluated on its ability to predict Clavien-Dindo class III and IV complications as well as Clavien-Dindo class IV complications alone.

Statistical analysis was performed as follows. Pearson Chi-square and Fisher's exact tests were used to assess categorical variables. Wilcoxon rank sum test was used to assess differences in continuous variables. Logistic regression modeling was performed with backwards stepwise selection with a $p < 0.2$. Final models adjusted for ASA class, wound class, patient age, operative time (as a surrogate for surgical complexity), performance of major concomitant procedure, obesity, route of surgery (MIS vs open), and inpatient status. C-statistic with 95 % CI was obtained post regression and used to evaluate the predictive ability of the mFI-5 score. A c-statistic of 0.5 was considered no better than chance, while a c-statistic of 0.7 or greater was considered strongly predictive of the given outcome measure. All statistics were performed with Stata 14.2 (College Station, TX).

3. Results

80,293 hysterectomies were identified, with 59,078 (73.6 %) benign and 21,215 (26.4 %) oncologic cases. Demographic data are depicted in Table 1. Patients undergoing benign hysterectomy were younger ($p = 0.001$), less likely to be obese ($p = 0.001$), and more likely to have a lower ASA class ($p = 0.001$). Their hysterectomies were more likely to be performed vaginally compared to the oncology group ($p = 0.001$) and were less likely to have infected/dirty wounds ($p = 0.001$). They had more outpatient procedures and shorter operative times ($p = 0.001$).

With regard to mFI-5 scores among the two groups, patients undergoing hysterectomy for malignant indications were more likely to have hypertension requiring medication, partially-dependent or dependent functional status, insulin-dependent diabetes, COPD, and congestive heart failure compared to the benign group (Table 2). They were also less likely to have an mFI-5 score of 0 (51.2 % vs 71.3 %, $p = 0.001$).

Frequencies of the primary outcome (30-day mortality) and secondary outcomes (readmission, major complications) as well as adjusted and unadjusted regressions are demonstrated in Table 3. In the benign group, there was a 0.03 % 30-day mortality rate; after adjusting for ASA class, wound class, patient age, operative time, obesity, performance of major concomitant procedure, route of surgery, and inpatient status, mFI-5 was a strong predictor of mortality ($c = 0.819$, CI 0.704–0.933). mFI-5 was moderately predictive of readmission ($c = 0.623$, CI 0.610–0.636) and major complication ($c = 0.603$, CI 0.594–0.613). Among benign cases, a 1-unit increase in mFI-5 score increased the odds of readmission and major complication by 4.7 times (CI 2.98–7.26) and 2.2 times (CI 1.55–3.09), respectively (Table 3).

Within the oncology group, there was a 0.3 % mortality rate. Similarly to the benign group, mFI-5 was a strong predictor of mortality ($c = 0.801$, CI 0.750–0.851), particularly for uterine cancer and cervical cancer ($c = 0.819$, CI 0.755–0.883 and $c = 0.962$, CI 0.892–1.0, respectively) (Table 3). It was moderately predictive of readmission for all the cancer groups collectively ($c = 0.671$, CI 0.656–0.686). When adjusted for ASA class, wound class, patient age, operative time, obesity, performance of major concomitant procedure, route of surgery, and inpatient status, a 1-unit increase in mFI-5 score increased odds of readmission by 2.7 times (CI 1.67–4.37) overall and 4.4 times (CI 2.47–7.82) in the uterine cancer subgroup. With regard to major complication, the mFI-5 was moderately predictive across the overall cancer group ($c = 0.690$, CI 0.677–0.703), however among the cervical and "other" cancer subgroups it was strongly predictive ($c = 0.711$, CI 0.678–0.743 and $c = 0.720$, CI 0.670–0.770, respectively). When

Table 1
Demographics.

	Benign N (%) or median (IQR)	Oncologic N (%) or median (IQR)	p-value
Age			
<40	11,347 (19.2)	1,609 (7.6)	0.001
40-60	38,989 (66.0)	8,442 (39.8)	
>60	8,742 (14.8)	11,164 (52.6)	
ASA class			0.001
1	5,870 (9.9)	503 (2.4)	
2	39,178 (66.4)	9,112 (43.0)	
3	13,592 (23.0)	10,758 (50.7)	
4	404 (0.7)	839 (4.0)	
5	5 (0.01)	1 (0.01)	
Race			0.001
Black	10,503 (17.8)	1,490 (7.0)	
White	38,220 (64.7)	14,818 (69.9)	
Asian	1,962 (3.3)	841 (4.0)	
Other/Unknown	8,393 (14.2)	4,066 (19.2)	
Hispanic	5,149 (8.7)	1,249 (5.9)	0.001
BMI			0.001
<18.5	429 (0.7)	230 (1.1)	
18.5–24.9	13,171 (22.3)	4,328 (20.4)	
25–29.9	17,102 (29.0)	4,991 (23.5)	
>30	28,376 (48.0)	11,666 (55.0)	
Preoperative albumin			0.001
Low (≤ 3.4)	970 (4.5)	1,079 (8.5)	
Normal (3.5–5.3)	20,542 (95.4)	11,594 (91.4)	
High (≥ 5.4)	28 (0.1)	6 (0.1)	
Hysterectomy Type			0.001
Open	15,073 (25.5)	7,655 (36.1)	
Laparoscopic	34,434 (58.3)	13,158 (62.0)	
Vaginal	9,571 (16.2)	402 (1.9)	
Performance of concomitant procedures			0.001
Y	2348 (4.0)	984 (4.6)	
N	56,730 (96.0)	20,231 (95.4)	
Procedural setting			0.001
Inpatient	27,842 (47.1)	12,805 (60.4)	
Outpatient	31,231 (52.9)	8,410 (39.6)	
Wound class			0.001
Clean/clean-contaminated	58,371 (98.8)	20,705 (97.6)	
Infected/Dirty	707 (1.2)	510 (2.4)	
Operative Time (min)	126 (93–171)	154 (113–208)	0.001
Cancer Type			
Uterine		13,359 (63.0)	
Cervical		2,733 (12.9)	
Ovarian		4,235 (20.0)	
Other*		888 (4.1)	

* Other includes GTN (6) Non-Gyn (479) Other-Gyn (353) Vaginal (25) Vulvar (25).

looking at the ability of the mFI-5 to specifically predict Clavien-Dindo Class III and IV complications within the oncology cohort, it was almost universally strongly predictive (Table 5). Among all cancer groups, there was a 2.6 increased odds of major complication with an increase in mFI-5 score when adjusted for the above confounders (CI 1.71–3.90). Within the cervical cancer and uterine cancer subgroups, an increase in mFI-5 score increased the odds of major complication by 4.2 times (CI 1.11–16.20) and 3.0 times (CI 1.75–5.21), respectively.

The results of our secondary analysis looking at the predictive value of mFI-5 at specific cut points for both benign and oncologic cohorts are shown in Table 4. The results are similar to the overall analysis; at a cutoff of 0.4 within the benign cohort, the mFI-5 was strongly predictive of mortality ($c = 0.815$, CI 0.699–0.931) and moderately predictive of readmission ($c = 0.621$, CI 0.608–0.634) and major complication ($c = 0.604$, CI 0.594–0.614). We were not able to assess the predictive value of the mFI-5 for mortality at a cutoff of 0.6 as none of the patients who died within 30 days of surgery met this cutoff. While a cutoff of 0.6 was moderately predictive of readmission and mortality, due to the very low number of patients that met this threshold, these results should be interpreted with caution. Within the oncology cohort, an mFI-5 score

Table 2
Distribution of mFI-5 Factors and mFI-5 scores among Benign and Oncologic Groups.

	BenignN (%)	OncologicN (%)	p-value
Functional status			
Independent	58,886 (99.74)	20,986 (98.96)	0.001
Partially dependent	131 (0.22)	199 (0.94)	
Dependent	24 (0.04)	22 (0.10)	
Insulin-dependent Diabetes	1,288 (2.2)	1,082 (5.1)	0.001
COPD	562 (1.0)	446 (2.1)	0.001
CHF within 30 days of surgery	50 (0.1)	80 (0.4)	0.001
HTN requiring medication	16,275 (27.6)	9,983 (47.1)	0.001
mFI-5 Score			0.001
0	42,096 (71.3)	10,852 (51.2)	
0.2	15,689 (26.6)	9,036 (42.6)	
0.25	15 (0.03)	4 (0.02)	
0.4	1,215 (2.1)	1,203 (5.7)	
0.5	0 (0.0)	2 (0.01)	
0.6	57 (0.1)	110 (0.5)	
0.75	0 (0.0)	1 (0.01)	
0.8	5 (0.01)	6 (0.03)	
1.0	1 (0.01)	1 (0.01)	

greater than or equal to 0.4 was strongly predictive of 30-day mortality (c = 0.799, CI 0.749–0.849) and moderately predictive of readmission (c = 0.670, CI 0.655–0.685) and major complication (c = 0.689, CI 0.676–0.702). Similar to the benign group, the number of patients meeting the 0.6 cutoff was very small, limiting our ability to assess the predictive value of mFI-5 in this group.

4. Discussion

Our results indicate that the mFI-5 is a strong-predictor of 30-day postoperative mortality and a good predictor of readmission and major complication following hysterectomy in both benign and oncologic patient populations.

The use of mFI-5 in gynecology literature is limited; to our knowledge, only three other studies have examined the use of mFI-5 in the

gynecologic surgery population. The initial study by Subramaniam et al (2018) that found the mFI-5 was equally predictive as mFI-11 for mortality, postoperative infection, and unplanned 30-day readmission across multiple surgical specialties. (Subramaniam et al., 2018) In this study, gynecology was examined as a composite group and not broken down into procedure type or benign/oncologic indication, however the remainder of our methodology was similar. In their 2012 and 2015 adjusted models, mFI-5 was strongly predictive of mortality (c = 0.807, CI 0.729–0.885 and c = 0.827, CI 0.762–0.891, respectively), although they noted that the low number of overall deaths resulted in parameter estimates that were unstable and therefore caution was recommended in interpreting these results. Our results similarly indicated that the mFI-5 is a strong predictor of mortality in benign gynecology and gynecologic oncology populations specifically for hysterectomy. While the number of deaths in both groups was also low in our study, the low mortality rate in gynecologic surgery will likely make this an unavoidable limitation in all research examining the link between frailty and postoperative mortality.

Major postoperative complication was the outcome that was most variable between our benign and oncology cohorts. Within the benign cohort, mFI-5 was weakest at predicting major complication compared to mortality and readmission (although still performed better than chance). It is possible this is due to the higher percentage of abdominal hysterectomies and concomitant procedures within the oncology cohort; in the Wainger et al) study looking at the effect of frailty on post-operative complications by type of hysterectomy, abdominal hysterectomy was associated with a higher risk of complication in frail patients. (Wainger et al., 2021) This speaks to a significant challenge when studying frailty’s association with surgical complications—specifically, the difficulty separating the degree to which complications are due to a patient’s frailty status versus inherent risks of the surgery itself. However, to try and account for this, we adjusted for route of hysterectomy and performance of concomitant procedures in our final model, with the above result. An alternative explanation for the discrepancy in predictive performance is that the low number of patients in the benign cohort who had major complications was small relative to the overall sample

Table 3
Unadjusted and Adjusted Regression for Benign and Oncologic Cases.

	PrevalenceN (%)	Unadjusted C-statisticC (95 % CI)	Adjusted C-statistic C* (95 % CI)	Unadjusted Odds ratioOR (95 % CI)	Adjusted Odds ratio aOR* (95 % CI)
30-day mortality					
Benign	20 (0.03)	0.584 (0.470–0.697)	0.819 (0.704–0.933)	18.60 (0.57–609.39)	0.33 (0.01–16.54)
Oncologic	Ovarian: 22 (0.52)Uterine: 33 (0.25)Cervical: 3 (0.11)Other: 5 (0.56)	0.603 (0.493–0.713)0.600 (0.515–0.680)	0.709 (0.607–0.811) 0.819 (0.755–0.883)	19.70 (0.93–415.89) 14.74 (1.40–155.24)	1.96 (0.06–66.87)3.58 (0.26–50.09)3.55 (0.01–616056)5.89 (0.01–5580)
	Overall: 63 (0.30)	0.611 (0.550–0.672)	0.712(0.365–1.000)	832.52 (2.22–312527)64.24 (0.15–28023)	3.09 (0.45–21.30)
			0.801(0.750–0.851)	18.17 (3.38–97.61)	
Readmission within 30 days of surgery					
Benign	1,881 (3.2)	0.528 (0.517–0.539)	0.623 (0.610–0.636)	4.07 (2.70–6.12)	4.65 (2.98–7.26)
Oncologic	Ovarian: 349 (8.2)Uterine: 666 (5.0)Cervical: 170 (6.2)Other: 94 (10.6)	0.515 (0.487–0.543)0.541 (0.521–0.562)0.497 (0.491–0.562)0.561 (0.443–0.550)	0.608 (0.577–0.639)0.672 (0.651–0.694)0.697 (0.656–0.738)0.629 (0.571–0.686)	1.86 (0.75–4.61) 4.40 (2.47–7.82)3.53 (0.92–13.58) (0.17–6.15)	1.68 (0.62–4.50) 3.91 (2.10–7.27)2.23 (0.43–11.51)0.65 (0.09–4.74)
	Overall: 1,279 (6.0)	0.517 (0.503–0.532)	0.671 (0.656–0.686)	2.15 (1.40–3.32)	2.71 (1.67–4.37)
Major complication					
Benign	3,503 (5.9)	0.514 (0.506–0.522)	0.603 (0.594–0.613)	2.27 (1.65–3.11)	2.19 (1.55–3.09)
Oncologic	Ovarian: 520 (12.3)Uterine: 904 (6.8)Cervical: 262 (9.6)Other: 115 (13.0)	0.528 (0.504–0.551)0.541 (0.523–0.559)0.535 (0.505–0.564)0.561 (0.511–0.610)	0.648 (0.623–0.674)0.681 (0.663–0.700) 0.711 (0.678–0.744) 0.720 (0.670–0.770)	2.64 (1.24–5.60) 4.35 (2.64–7.19) 5.31 (1.79–15.75) 6.29 (1.34–29.39)	1.37 (0.60–3.16) 3.02 (1.75–5.21) 4.24 (1.11–16.20)4.24 (0.72–25.08)
	Overall: 1,801 (8.5)	0.522 (0.510–0.535)	0.690 (0.677–0.703)	2.44 (1.68–3.53)	2.58 (1.71–3.90)

Major complication includes composite of: septic shock, cardiac arrest, unplanned reintubation, reoperation, surgical site infection, wound or vaginal cuff dehiscence, pneumonia, PE, DVT, UTI, transfusion, MI, acute renal failure, CVA.

* Adjusted for ASA, Wound classification, Age, Operating time/Surgical complexity, obesity, route of surgery (MIS vs open), major concomitant procedure, and inpatient status.

Table 4
Adjusted Regression for Benign and Oncologic Cases using mFI-5 cutoffs.

mFI-5 Cut-Off		Prevalence N (% of patients within the cutoff criteria)	Adjusted C-statistic C (95 % CI)
mFI-5 >/= 0.4	30-day Mortality		
	<i>Benign</i>	1 (5)	0.815 (0.699–0.931)
	<i>Oncologic</i>	Ovarian: 2 (9.1)	0.706 (0.605–0.806)
		Uterine: 4 (12.1)	0.814 (0.750–0.878)
		Cervical: 0 (0.0)	N/A
		Other: 1 (20.0)	0.734 (0.390–1.000)
	Overall: 7 (11.1)	0.799 (0.749–0.849)	
	Readmission		
	<i>Benign</i>	87 (4.6)	0.621 (0.608–0.634)
	<i>Oncologic</i>	Ovarian: 18 (5.2)	0.608 (0.577–0.639)
		Uterine: 77 (11.6)	0.671 (0.649–0.693)
		Cervical: 9 (5.3)	0.696 (0.654–0.737)
Other: 6 (6.4)		0.629 (0.571–0.687)	
Overall: 110 (8.6)		0.670 (0.655–0.685)	
Major complication			
<i>Benign</i>	136 (3.9)	0.604 (0.594–0.614)	
<i>Oncologic</i>	Ovarian: 30 (5.8)	0.647 (0.622–0.673)	
	Uterine: 110 (12.2)	0.681 (0.663–0.699)	
	Cervical: 16 (6.1)	0.709 (0.676–0.741)	
	Other: 8 (7.0)	0.712 (0.661–0.762)	
	Overall: 164 (9.1)	0.689 (0.676–0.702)	
mFI-5 >/= 0.6	30-day Mortality		
	<i>Benign</i>	0 (0)	N/A
	<i>Oncologic</i>	Ovarian: 0 (0.0)	N/A
		Uterine: 1 (3.0)	0.813 (0.747–0.880)
		Cervical: 0 (0.0)	N/A
		Other: 0 (0.0)	N/A
	Overall: 1 (1.6)	0.799 (0.748–0.849)	
	Readmission		
	<i>Benign</i>	11 (0.6)	0.616 (0.603–0.630)
	<i>Oncologic</i>	Ovarian: 3 (0.9)	0.609 (0.578–0.640)
		Uterine: 16 (2.4)	0.671 (0.649–0.693)
		Cervical: 1 (0.6)	0.695 (0.654–0.736)
Other: 0 (0.0)		N/A	
Overall: 20 (1.6)	0.671 (0.656–0.686)		
Major Complication			
<i>Benign</i>	14 (0.4)	0.601 (0.592–0.611)	
<i>Oncologic</i>	Ovarian: 2 (0.4)	0.648 (0.623–0.674)	
	Uterine: 22 (2.4)	0.682 (0.663–0.700)	
	Cervical: 2 (0.8)	0.708 (0.675–0.741)	
	Other: 0 (0.0)	N/A	
Overall: 26 (1.4)	0.690 (0.677–0.703)		

*Adjusted for ASA, Wound classification, Age, Operating time/Surgical complexity, obesity, route of surgery (MIS vs open), major concomitant procedure, and inpatient status.

Table 5
Predictive Ability of mFI-5 for Clavien-Dindo Class III and IV complications Among Oncology Cohort.

	Oncology cohort N (%)	Adjusted C-statistic C (95 % CI)
Clavien-Dindo Class III or IV complication	Ovarian: 236 (5.6)	0.669 (0.632–0.705)
	Uterine: 372 (2.8)	0.733 (0.706–0.760)
	Cervical: 78 (2.9)	0.731 (0.672–0.789)
	Other: 58 (6.5)	0.746 (0.681–0.810)
	Overall: 744 (3.5)	0.732 (0.713–0.750)
Clavien-Dindo Class IV complication	Ovarian: 145 (3.4)	0.720 (0.678–0.762)
	Uterine: 208 (1.6)	0.766 (0.734–0.798)
	Cervical: 28 (1.0)	0.831 (0.737–0.925)
	Other: 25 (2.8)	0.719 (0.625–0.813)
	Overall: 406 (1.9)	0.773 (0.751–0.795)

Clavien III (requiring surgical intervention): reoperation, wound dehiscence, vaginal cuff dehiscence.

Clavien IV (requiring ICU admission): septic shock, cardiac arrest, unplanned reintubation, pulmonary embolism, MI, CVA.

size (5.9 %) and may have limited our ability to assess the true predictive value of the mFI-5 in this setting. Within our oncology cohort, the mFI-5 approached being strongly predictive across the collective cancer group and was strongly predictive for cervical cancer and “other” cancer subgroups. However, when we narrowed the analysis to look at its ability to predict the most serious Clavien-Dindo Class IV complications, it was universally strongly predictive across each cancer subtype. These results suggest that mFI-5 may be more useful for predicting major complications within the gynecologic oncology patient population than the benign gynecology population, and that it is especially effective in predicting the most severe complications.

It is interesting that the predictive value of mFI-5 for all three outcome measures, particularly within the mortality and major complication measures, varied by cancer subtype. As mentioned above, mFI-5 was most predictive of mortality within the uterine and cervical cancer subgroups and most predictive of major complication within the cervical cancer and other cancer subgroups. Overall, mFI-5 appears to have been the least predictive of outcomes in the ovarian cancer subgroup, which was somewhat surprising given that the two other studies looking at frailty in gynecologic surgery (which both included ovarian cancer patients, although did not examine these patients as a subgroup) found an association between frailty and complication risk. (Wainger et al., 2021; Mah et al., 2022) We hypothesize this may be a result of our inability to distinguish stage and those undergoing hysterectomy as part of a primary debulking versus interval debulking following neoadjuvant chemotherapy. This distinction is potentially significant, given that those undergoing a primary debulking may be having a more aggressive procedure with inherently increased risk of death and complications, and stage is independently predictive of postoperative complications per the findings in Mah et al (Mah et al., 2022). It is possible that a patient’s ability to withstand a radical procedure without postoperative mortality and complication is at least in part related to their degree of frailty preoperatively; the recent study by Handley et al (2022) demonstrating that frail patients are less likely to be offered surgical management for ovarian cancer indicates that surgeons agree with this hypothesis. (Handley et al., 2022) Our theory is further supported by the predictive ability of mFI-5 for mortality in cervical cancer; this was the one cancer

subgroup and outcome measure for which both the adjusted and unadjusted models were strongly predictive, and the adjusted model provided the best predictive value of the study at a c-statistic of 0.962. One explanation may be that since most cervical cancer patients undergoing surgical management are more likely to have some form of radical hysterectomy per NCCN guidelines, (Network and Clinical Practice Guidelines, 2020) the increased complexity and invasiveness of the procedure compared to traditional hysterectomy makes preoperative frailty of the patient especially important in predicting mortality post-operatively. While further study is needed as to the role of mFI-5 in determining candidacy for radical cancer procedures, our results suggest that it could be a helpful adjunct tool for gynecologic oncologists in selecting up front treatment options; patients who are poor surgical candidates for radical surgery based on frailty score may benefit from alternatives to surgery such as neoadjuvant chemotherapy and radiotherapy. In those for whom there is no alternative to surgery, the mFI-5 could also help identify those who may benefit from closer follow up.

When considering the practical applications of the mFI-5, one of the biggest advantages is the feasibility of use in everyday clinical practice compared to other frailty scoring systems available. While other scoring options can contain up to 30 and 40 factors, the mFI-5 requires only 5 easily-captured baseline health factors that are readily identifiable from either chart review or patient-provided history. (Orlandini et al., 2020; Kumar et al., 2017) A recently published review of 6 frailty assessment tools, including the original mFI-11, identified the mFI-11 as the most utilized and the most practical. (Di Donato et al., 2021) It follows therefore that a validated scoring system with six fewer factors would only improve the ease of clinical use, with the added benefit of not having to sacrifice predictive value. Having a simple, fast scoring system available that clinicians actually use could then improve our ability to identify patients who can benefit from “prehabilitation” prior to surgery, which previous studies have indicated is both effective and cost-saving. (Schneider et al., 2020; Gillis et al., 2018; Dholakia et al., 2021) Future use of the mFI-5 in gynecologic surgery could incorporate the scoring system into the electronic medical record for additional convenience and prospective study.

The primary strength of our study lies in the large number of patients from a regularly-audited database incorporating data from hundreds of hospitals, suggesting good generalizability of our results. Furthermore, ours is the first study to categorize our results by indication for surgery and cancer subtype, allowing us to better identify which groups may benefit the most from a preoperative frailty tool. Our study has the inherent weaknesses of a retrospective design. Furthermore, there were limitations to the database itself, including the potential for misclassification bias, our inability to determine timing of hysterectomy for ovarian cancer, and a missing functional status in the database for 22 patients (although our calculation method still enabled us to include them). Finally, the overall number of deaths in both benign and oncologic groups was low in this large cohort, thus the mortality data should be interpreted with caution.

Our study found that the mFI-5, comprised of 5 easily-identifiable health factors, is a strong predictor of 30-day mortality and moderate predictor of readmission and major complications following hysterectomy in both benign and oncologic patient populations. Notably, its predictive ability varied by gynecologic cancer type, however among all cancer types it was strongly predictive of the most serious complications. These findings have the potential to improve identification of high-risk patients in the preoperative setting, providing an opportunity for preoperative medical optimization and enhanced postoperative monitoring and follow up. Furthermore, they identify potential areas for future study, including the use of the mFI-5 in determining candidacy for radical gynecologic surgery.

Author contributions

Study Design: Hermann, Koelper, Latif, Ko.

Data Collection: Hermann and Koelper.

Data Analysis: Hermann, Koelper, Andriani, Ko.

Drafting of Manuscript: Hermann, Ko.

Manuscript Revision: Hermann, Koelper, Andriani, Latif, Ko.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Dr. Ko reports the following relationship with Tesaro: Associated Research Support to Institution for Clinical Trial. However, there was no relevance to this project. The remaining authors have no disclosures].

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References

- Buckingham, L., Cory, L., Brensigner, C., Zhang, X., et al., 2020. Epidemiologic profile of benign versus oncologic gynecology populations: similar procedures, different patients. *Eur. J. Gynecol. Oncol.* 41 (3), 396–401.
- Clavien, P.A., Barkun, J., de Oliveira, M.L., Vauthey, J.N., et al., 2009. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg.* 250 (2), 187–196.
- Courtney-Brooks, M., Tellawi, A.R., Scalici, J., Duska, L.R., et al., 2012. Frailty: an outcome predictor for elderly gynecologic oncology patients. *Gynecol. Oncol.* 126 (1), 20–24.
- Dholakia, J., Cohn, D.E., Straughn Jr, J.M., Dille, S.E., 2021. Prehabilitation for medically frail patients undergoing surgery for epithelial ovarian cancer: a cost-effectiveness analysis. *J. Gynecol. Oncol.* 32 (6), e92.i.
- Di Donato, V., Caruso, G., Bogani, G., Giannini, A., et al., 2021. Preoperative frailty assessment in patients undergoing gynecologic oncology surgery: a systematic review. *Gynecol. Oncol.* S0090-9258(20)34245-1. Online ahead of print.
- Dindo, D., Demartines, N., Clavien, P.A., 2004. Classification of Surgical Complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann. Surg.* 240 (2), 205–213.
- Driver, J.A., Viswanathan, A.N., 2017 Jun. Frailty measure is more predictive of outcomes after curative therapy for endometrial cancer than traditional risk factors in women 60 and older. *Gynecol. Oncol.* 145 (3), 526–530.
- Erekson, E.A., Yip, S.O., Ciarleglio, M.M., Fried, T.R., 2011. Postoperative complications after gynecologic surgery. *Obstet. Gynecol.* 118 (4), 785–793.
- George, E.M., Burke, W.M., Hou, J.Y., Tergas, A.L., et al., 2016. Measurement and validation of frailty as a predictor of outcomes in women undergoing major gynaecological surgery. *BJOG* 123 (3), 455–461.
- Gillis, C., Buhler, K., Bresee, L., Carli, F., et al., 2018. Effects of nutritional prehabilitation, with and without exercise, on outcomes of patients who undergo colorectal surgery: a systematic review and meta-analysis. *Gastroenterology* 155 (2), 391–410.
- Handley, K.F., Sood, A.K., Dal Molin, G.Z., Westin, S.M., et al., 2022. Frailty repels the knife: the impact of frailty index on surgical interventions and outcomes. *Gynecol. Oncol.*
- Kumar, A., Langstraat, C.L., DeJong, S.R., McGree, M.E., 2017. Functional not chronological age: frailty index predicts outcomes in advanced ovarian cancer. *Gynecol. Oncol.* 147 (1), 104–109.
- Mah, S.J., Anpalagan, T., Marcucci, M., Eiriksson, L., et al., 2022. The five-factor modified frailty index predicts adverse postoperative and chemotherapy outcomes in gynecologic oncology. *Gynecol. Oncol.*
- Mullen, M.M., Porcellini, B.P., Cripe, J., Massad, L.S., Kuroki, L.M., et al., 2020. Modified frailty index is predictive of wound complications in obese patients undergoing gynecologic surgery via a midline vertical incision. *Gynecol. Oncol.* 157 (1), 287–292.
- National Comprehensive Cancer Network, 2020. NCCN Clinical Practice Guidelines in Oncology: Cervical Cancer. Version 1.2021. Oct 27. https://www.nccn.org/practiceguidelines/physician_gls/pdf/cervical_blocks.pdf. Accessed Jan 10, 2021.
- Orlandini, L., Nestola, T., Colloca, G.F., Ferrini, A., et al., 2020. The frailty index in older women with gynecological cancer. *Aging Clin. Exp. Res.* 32 (8), 1561–1565.
- Schneider, S., Armbrust, R., Spies, C., du Bois, A., et al., 2020. Prehabilitation programs and ERAS protocols in gynecological oncology: a comprehensive review. *Arch. Gynecol. Obstet.* 301 (2), 315–326.
- Sia, T., Wen, T., Cham, S., Friedman, A., 2020. Effect of frailty on postoperative readmissions and cost of care for ovarian cancer. *Gynecol. Oncol.* 159 (2), 426–433.
- Subramaniam, S., Aalberg, J.J., Soriano, R.P., Divino, C.M., 2018. New 5-factor modified frailty index using American College of Surgeons NSQIP data. *J. Am. Coll. Surg.* 226 (2), 173–181.
- Suskind, A.M., Jin, C., Walter, L.C., Finlayson, E., 2017. Frailty and the role of obliterative versus reconstructive surgery for pelvic organ prolapse: a national study. *J. Urol.* 197 (6), 1502–11506.

- Uppal, S., Ige, R., Rice, L.W., Spencer, R.J., Rose, S.L., 2015. Frailty index predicts severe complications in gynecologic oncology patients. *Gynecol Oncol.* 137 (1), 98–101.
- Velanovich, V., Antoine, H., Swartz, A., Peters, D., et al., 2013. Accumulating deficits model of frailty and postoperative mortality and morbidity: its application to a national database. *J. Surg. Res.* 183 (1), 104–110.
- Wainger, J.J., Yazdy, G.M., Handa, V.L., 2021. Abdominal hysterectomy and high frailty score are associated with complications among older patients. *Int. J. Gynecol. Obstet.* 00, 1–7.
- Wilkes, J.G., Evans, J.L., Prato, B.S., Hess, S.A., et al., 2019. Frailty cost: economic impact of frailty in the elective surgical patient. *J. Am. Coll. Surg.* 228 (6), 861–870.