Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Utilizing Combined Prognostic Indices to Guide Decision-Making for Optimal Patient Care in Colorectal Cancer Screening Colonoscopies

Alexander M. Sy

alexander.sy3@va.gov

Bruce W. Carter VA Medical Center

Mehak Sharma

Bruce W. Carter VA Medical Center

Adriana Medina

Bruce W. Carter VA Medical Center

Ignacia Dalmacio

Bruce W. Carter VA Medical Center

Gema Casco

Bruce W. Carter VA Medical Center

Laura Y. Tirse

Bruce W. Carter VA Medical Center

Flavia Carneiro

Bruce W. Carter VA Medical Center

Mina Shaker

Bruce W. Carter VA Medical Center

Short Report

Keywords: Age-adjusted Charlson Comorbidity Index (ACCI), VA-Frailty Index (VA-FI), comorbidity, frailty, mortality, screening colonoscopy

Posted Date: November 25th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11695328/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Purpose:

To determine whether combining the age-adjusted Charlson Comorbidity Index (ACCI) and Veterans Affairs Frailty Index (VA-FI) improves prediction of long-term mortality among veterans undergoing screening colonoscopy.

Methods:

This retrospective cohort included 705 veterans undergoing screening colonoscopy at two Veterans Affairs facilities during 2013–2014, with follow-up through June 30, 2026. Baseline ACCI and VA–FI scores were calculated from clinical records. High comorbidity and elevated frailty were defined as ACCI ≥ 5 and VA–FI > 0.10, respectively. Mortality associations were evaluated using logistics and Cox regression. Discrimination was assessed using receiver operating characteristic curves, bootstrap comparisons, and cross-validation.

Results:

During follow-up of up to 13.5 years, 154 veterans (21.8%) died. ACCI and VA-FI were moderately correlated (Spearman ρ = 0.50, p < 0.0001). Combining both indices increased the area under the curve from 0.721 for ACCI alone to 0.737, an absolute improvement of 0.016 (95% confidence interval, 0.004–0.034). Cross–validated discrimination was similar (0.731). After adjustment for sex, body mass index, and other index, mortality hazard increased with each ACCI point (hazard ratio, 1.31) and each 0.10–unit VA–FI increase (hazard ratio, 1.73). Among veterans with ACCI < 5, mortality was 32.0% with elevated frailty versus 15.1% without elevated frailty.

Conclusion:

Comorbidity and frailty provided complementary prognostic information after screening colonoscopy. Adding VA–FI to ACCI modestly improve mortality discrimination, with additional risk stratification among veterans with lower comorbidities scores. External validation and studies evaluating screening benefits and harms are needed before these indices can guide individualized colorectal cancer screening decisions.

Introduction

Cancer screening decision-making is complex, balancing benefits and harms, especially for older adults, individuals with frailty, and those with multiple comorbidities. The current Multi-Society Guideline on Colorectal Cancer Screening recommends considering health status, prior negative screening results,

and life expectancy when deciding whether to undergo colorectal cancer screening and follow-up.[1] Decision-making is complicated because no prognostic indicator currently guides it. It relies heavily on physician judgment, which may reflect uncertainty about the benefits versus harms of screening and follow-up colonoscopies, leading to overuse of these procedures, even when life expectancy is limited and colon cancer prevention offers no benefit.

In a study of 75-year-older adults, 30% had a life expectancy of less than 10 years and had undergone screening colonoscopies, which were associated with an increased risk of complications.[2] A separate study found that age and comorbidity predicted death in older adults who underwent colonoscopy.[3] Another study found that frail elderly individuals have a higher risk of colonoscopy complications than their non-frail counterparts.[4,5] However, younger adults under 65 are also experiencing chronic conditions and frailty. Data from 2023 showed that about 130 million US adults (51.4%) have multiple chronic conditions, and of these, 63.8 million (52.7%) were aged 35-64.[6] Studies have also shown that frailty is prevalent in younger adults.[7,8] As the rates of obesity, depression, diabetes, chronic kidney disease (CKD), and stroke increase, leading to long-term morbidity, the protective effect of younger age diminishes as comorbidity increases.[6] Thus, long-term prognosis is essential for guiding preventive care.

The Charlson Comorbidity Index (CCI) includes 19 comorbidities to predict one-year mortality. [9] A study using this index found that individuals with higher comorbidity levels generally have shorter life expectancies. Conversely, those without comorbid conditions, including older adults, tend to have longer life expectancies than the average person of the same age, making it a useful tool for personalizing recommendations on whether to stop or continue preventive testing.[10] Since age has been shown to correlate with survival, the CCI was modified to include age; thus, the age-adjusted Charlson comorbidity index (ACCI) was developed. [11] Although the ACCI covers various comorbidities, it cannot account for all patient factors, such as functional, cognitive, and mental health status. Multiple studies have shown that frailty is a strong and independent predictor of mortality across different populations, including both older and younger groups. [12–14] A prospective study showed that frailty status predicts adverse events during colonoscopy better than age and the CCI. [5] The Department of Veterans Affairs developed a frailty scoring system, the VA-Frailty Index (VA-FI), which incorporates 31 health deficits. [15] The VA-FI has been studied and validated for predicting mortality in hematologic malignancies and non-cardiac surgeries, as well as for identifying morbidity in pre-surgical screening. [16–19] The primary aim of this study is to determine whether combining two prognostic indices improves mortality assessment to support decisions about screening colonoscopy. We hypothesize that the VA-FI and the ACCI capture complementary prognostic information, and that a model combining both would discriminate all-cause mortality after screening colonoscopy better than either index alone.

Patients and Methods

Study Design

This retrospective review examined records of screening colonoscopies performed at the Bruce Carter VA Medical Center and the William “Bill” Kling VA Clinic from January 1, 2013, to December 31, 2014. All research was conducted in accordance with the Declaration of Helsinki and with approval from the participating Veterans Affairs (VA) medical centers' Institutional Review Boards. Informed consent was waived.

Patient population:

Eligible adult veterans who underwent screening colonoscopies ordered between January 1, 2013, and December 31, 2014, were included in the review. Duplicate orders, screening colonoscopies intended for diagnostic purposes, and cases with incomplete or missing data were excluded. Seven records with missing data were excluded, and analyses were conducted on complete cases. No imputation was performed. Using the VA’s electronic health record, the Computerized Patient Record System (CPRS), we obtained baseline demographics (sex, age, and BMI at the time of colonoscopy), anesthesia used during the colonoscopy, and colonoscopy findings. We categorized age as < 50, 50–59 years, 60–69 years, 70–79 years, and ≥ 80 years. Body mass index was grouped as < 18.5, 18.5–24.9, 25–29.9, 30–34.9, 35–39.9, and > 40. Anesthesia was categorized as MAC, moderate sedation, or no anesthesia. Colonoscopy findings were classified as normal, adenoma, high-risk polyps, colon cancer, or abnormal findings. We followed veterans until June 30, 2026, and recorded their vital status (alive or deceased). Veterans’ comorbidity and frailty data were derived from diagnosis codes and a look-back period using available clinical notes at the time of the colonoscopy. We then calculated the ACCI and VA-FI for each veteran **(Fig. 1).** A VA-FI > 0.10 indicated frailty, and an ACCI ≥ 5 indicated high comorbidity.

Figure 1: Flow Diagram

731 Screening colonoscopies

January 1, 2013 – December 31, 2014

Excluded: 26

Duplicate orders: 14

Diagnostic colonoscopy: 5

Missing data: 7

705 Screening colonoscopies

January 1, 2013 – December 31, 2014

Age, Sex, BMI, colonoscopy findings, anesthesia used,

Age-adjusted Charlson Comorbidity Index and VA Frailty Index Scores

Followed for 13.5 years

Alive = 551 vs Deceased = 154

Statistical Analysis:

Descriptive statistics were compared between the alive and deceased groups. Categorical variables were summarized as frequencies and percentages and compared across vital status groups using the Pearson chi-square test, with Fisher's exact test used when expected cell counts were small. Continuous variables were summarized as mean (standard deviation) and median (interquartile range) and compared between survivors and decedents using the Mann-Whitney U test. Associations among continuous variables (ACCI, VA-FI, age) were assessed using Pearson and Spearman correlation coefficients. Age group and BMI category were treated as ordinal categories; anesthesia type was treated as nominal.

No formal sample size calculation was performed. The sample size was based on the number of eligible screening colonoscopies conducted at the participating VA medical centers from January 1, 2013, to December 31, 2014 (705 veterans after exclusions). With 154 deaths and a maximum of five parameters in any multivariable model (ACCI, VA-FI, sex, BMI category, and age group in sensitivity analyses), the cohort provided at least 30 events per parameter, which exceeds the commonly used threshold of 10 events per variable for logistic and Cox regression.

Predictive performance for mortality (death by June 30, 2026 was ascertained from the CPRS; all survivors were alive at the end of follow-up, and none were lost to follow-up, with up to 13.5 years of follow-up) was evaluated using logistic regression. Because age is already incorporated in the ACCI, it was not added to models containing the ACCI, except in prespecified sensitivity analyses. All continuous predictors were standardized (z-scored) before model fitting to enable direct comparison of effect sizes across variables measured on different scales. Discrimination was quantified using the area under the receiver operating characteristic (ROC) curve (AUC). Ninety-five percent confidence intervals for AUC and p-values for pairwise AUC differences between models were derived from 3,000 nonparametric bootstrap resamples of the cohort, with paired resampling used for model comparisons (identical resampled indices applied to competing models' predicted probabilities). Apparent AUCs were compared with 10-fold cross-validated AUCs (20 repeats). For nested models, improvement in model fit was tested using the likelihood-ratio (LR) test, comparing − 2 log-likelihoods between reduced and full models against a chi-square distribution with degrees of freedom equal to the difference in the number of parameters. The Akaike Information Criterion (AIC) was used to compare non-nested models for which a formal LR test was not applicable. Time to death, measured from the index colonoscopy to death or censoring on June 30, 2026, was analyzed using Kaplan-Meier estimates (log-rank test across VA-FI categories) and Cox proportional hazards models (Breslow method for tied event times; death dates were available only to the month). Hazard ratios are reported per ACCI point, per 0.10 increase in VA-FI, and per age group. Adjusted models included ACCI, VA-FI, sex, and BMI category. The proportional-

hazards assumption was assessed by testing interactions between covariates and follow-up period (≤ 5 vs. > 5 years).

To limit bias, ACCI and VA-FI were calculated from data recorded at or before the index colonoscopy, so exposure was measured before death. All screening colonoscopies during the period were reviewed consecutively, and reviewers abstracted records using a standard data form. Death is an objective outcome, which limits outcome misclassification. Residual confounding, selection from a single-region, predominantly male veteran population, and unmeasured factors such as smoking and socioeconomic status could not be excluded.

All statistical analyses were conducted using SAS v9.4 (SAS Institute Inc., Cary, NC, USA) and Stata v15 (StataCorp, College Station, TX, USA). A two-sided p-value < 0.05 was considered statistically significant. No multiple-comparison correction was applied because the comparisons were pre-specified and hierarchical (single predictors followed by nested combinations).

Results

Patient's Characteristics:

Seven hundred thirty-one records were reviewed from January 1, 2013, to December 31, 2014, and 26 were excluded. Of 705 patients with complete data, 551 (78.2%) were alive at the last follow-up, and 154 (21.8%) were deceased. The cohort included 622 males (88%); most patients were aged 50–69 years (88.7%), received moderate sedation (600; 85.1%), and had normal colonoscopy findings (97.7%). The mean and median ACCI were 2.45 ± 1.46 and 2, respectively. The mean VA-FI was 0.083 ± 0.054 (median 0.06). By VA-FI category, 73.3% of patients were non-frail and 26.7% were frail **(**Table 1**).**

One hundred fifty-four deaths (21.8%) occurred during follow-up of up to 13.5 years; 130 patients (18.4%) had a recorded death within 10 years. Deceased patients had higher ACCI (median 3 vs 2), higher VA-FI (median 0.10 vs 0.06), and lower ACCI-predicted 10-year survival (median 77% vs 90%) than survivors (Mann–Whitney $p < 0.001$ for each). Elevated frailty (VA-FI > 0.10) was associated with a 2.7-fold higher unadjusted odds of death (35.6% vs 16.8%; OR 2.74; 95% CI 1.88–3.99; $p < 0.001$). Female sex was associated with lower mortality (Fisher exact OR 0.35, $p = 0.003$), and this association persisted after adjustment (HR 0.47, $p = 0.039$). However, with only 83 women, this should be interpreted cautiously **(**Table 1**).**

Table 1
Cohort characteristics and mortality by subgroup

Variable	N (%)	Deaths	Mortality	p value
Overall cohort	705	154	21.8%	
Sex				**0.003 (Fisher)**
Male	622 (88.2%)	146	23.5%	
Female	83 (11.8%)	8	9.6%	
Age, years				**< 0.001 (χ^2)**
< 50	20 (2.8%)	1	5.0%	
50–59	352 (49.9%)	53	15.1%	
60–69	273 (38.7%)	69	25.3%	
70–79	56 (7.9%)	28	50.0%	
≥ 80	4 (0.6%)	3	75.0%	
BMI, kg/m²				**0.46**
< 18.5	20 (2.8%)	—	—	
18.5–24.9	224 (31.8%)	—	—	
25–29.9	265 (37.6%)	—	—	
30–34.9	133 (18.9%)	—	—	
35–39.9	42 (6.0%)	—	—	
> 40	21 (3.0%)	—	—	
ACCI	Mean (SD) 2.45 (1.46); median (IQR) 2 (1–3); range 0–11			**< 0.001**
0–2	410 (58.2%)	44	10.7%	
3	166 (23.5%)	49	29.5%	
4	71 (10.1%)	30	42.2%	
≥ 5	58 (8.2%)	31	53.4%	
VA-FI	Mean (SD) 0.083 (0.054); median (IQR) 0.06 (0.03–0.13); range 0–0.29			**< 0.001 (χ^2)**
≤ 0.10 (non-frail)	517 (73.3%)	87	16.8%	
> 0.10–0.20 (frail)	172 (24.4%)	57	33.1%	

Variable	N (%)	Deaths	Mortality	p value
> 0.20–0.30 (frail)	16 (2.3%)	10	62.5%	
> 0.30–0.40 (frail)	0	—	—	
> 0.40 (frail)	0	—	—	
Anesthesia				**0.21**
Moderate sedation	600 (85.1%)	—	—	
MAC	44 (6.2%)	—	—	
No anesthesia	61 (8.7%)	—	—	
Colonoscopy findings				
Normal	689 (97.7%)	150	21.8%	
Adenoma	13	3	23.1%	
1–2 adenomas	12	3	25.0%	
5–10 adenomas	1	0	—	
High-risk polyp	1	0	—	
Colitis	1	1	—	
AVM	1	0	—	
Colon cancer	0	0	—	
Time from colonoscopy to death				
< 12 months	—	15	—	
1 to < 5 years	—	38	—	
5–10 years	—	77	—	
> 10 years	—	24	—	

Percentages in the N column are column percentages of the 705 patients; mortality is deaths divided by N within each category. Time from colonoscopy to death is shown for the 154 decedents only. ACCI, age-adjusted Charlson Comorbidity Index; VA-FI, Veterans Affairs Frailty Index; BMI, body mass index; MAC, monitored anesthesia care; AVM, arteriovenous malformation; SD, standard deviation; IQR, interquartile range.

Relationship Between ACCI, VA-FI and Age

ACCI was substantially more correlated with patient age (Pearson r = 0.532, Spearman ρ = 0.606; both p < 0.001) than VA-FI (r = 0.195, ρ = 0.204; both p < 0.001), consistent with ACCI's age-weighted design (Table 2). ACCI and VA-FI were only moderately correlated with each other (r = 0.472, ρ = 0.497; p < 0.001), indicating substantial non-overlapping information between the two indices.

Table 2
Pearson and Spearman correlation among ACCI, VA-Fi, and Age

Relationship	Pearson Correlation (r)	Spearman Correlation (p)	p-value
ACCI ↔ age group	0.532	0.606	< 0.001
VA-FI ↔ age group	0.195	0.204	< 0.001
ACCI score ↔ VA FI	0.472	0.497	< 0.001

Predictive Performance: Logistic Regression and AUC

In univariable logistic regression, ACCI alone discriminated mortality with an AUC of 0.721 (95% CI, 0.68–0.77), compared with 0.674 (95% CI, 0.63–0.72) for VA-FI alone and 0.643 (95% CI, 0.60–0.69) for age alone (Table 3, Fig. 2). Because ACCI's apparent advantage over VA-FI could reflect its embedded age information rather than superior frailty assessment, a model combining VA-FI with age as an explicit covariate was fit; this model achieved an AUC of 0.715 (95% CI, 0.67–0.76), which was statistically indistinguishable from ACCI alone (difference − 0.006; 95% CI, − 0.043 to 0.034; p = 0.76). A model combining ACCI and VA-FI achieved the highest discrimination among two-predictor models, with an AUC of 0.737 (95% CI, 0.69–0.78). This represented an absolute gain of 0.016 over ACCI alone (95% CI, 0.004 to 0.034; p = 0.044) and of 0.062 over VA-FI alone (95% CI, 0.031–0.102; p < 0.001). Ten-fold cross-validated AUCs were similar to the apparent values (ACCI 0.711, VA-FI 0.666, ACCI + VA-FI 0.731).

Both ACCI and VA-FI independently predicted mortality. In the adjusted Cox model, each additional ACCI point was associated with a 31% higher hazard of death (HR 1.31), and each 0.10-unit increase in VA-FI was associated with a 73% higher hazard (HR 1.73), after mutual adjustment for each other, sex, and BMI. We deliberately omitted a separate age term from the adjusted models to avoid double-counting age, which is already incorporated in the ACCI. In a sensitivity analysis that added age group, VA-FI remained associated with mortality (HR 1.75; 95% CI 1.30–2.37), whereas the association with female sex was attenuated (HR 0.49; 95% CI 0.24–1.01; p = 0.053). There was no evidence of non-proportional hazards (global test for covariate × follow-up period interactions, p = 0.70). Kaplan-Meier survival analysis showed a statistically significant difference in overall survival across VA-FI categories (log-rank $\chi^2 = 45.10$, df = 2, p < 0.001), with progressively lower survival among patients with higher VA-FI scores (Fig. 3).

Table 3
Discrimination (AUC) from logistic regression and hazard ratios (HR) from Cox models

Model	Measure	Estimate (95% CI)	P value
Discrimination: area under the ROC curve (logistic regression)			
Age alone	AUC	0.643 (0.60–0.69)	
VA-FI alone	AUC	0.674 (0.63–0.72)	
ACCI alone	AUC	0.721 (0.68–0.77)	
VA-FI + age (comparison with ACCI, which includes age)	AUC	0.715 (0.67–0.76)	
ACCI + VA-FI	AUC	0.737 (0.69–0.78)	
ACCI + VA-FI + age (sensitivity)	AUC	0.740 (0.69–0.79)	
Hazard ratios (Cox proportional hazards models)			
Univariate	ACCI, per point	1.41 (1.31–1.51)	< 0.001
Univariate	VA-FI, per 0.10	2.47 (1.91–3.21)	< 0.001
Univariate	Age, per group	2.05 (1.66–2.52)	< 0.001
ACCI + VA-FI	ACCI, per point	1.32 (1.21–1.44)	< 0.001
ACCI + VA-FI	VA-FI, per 0.10	1.74 (1.30–2.33)	0.0002
Fully adjusted*	ACCI (includes age), per point	1.31 (1.20–1.43)	< 0.001
Fully adjusted*	VA-FI, per 0.10	1.73 (1.29–2.33)	0.0003
Fully adjusted*	Female sex	0.47 (0.23–0.96)	0.039
Fully adjusted*	BMI, per group	1.06 (0.91–1.23)	0.46

*Adjusted for ACCI (which includes age), VA-FI, sex, and BMI category. Hazard ratios from Cox proportional hazards models; follow-up ended June 30, 2026.

Ten-year survival declined from 86.1% (VA-FI ≤ 0.10) to 72.1% (VA-FI > 0.10–0.20) to 37.5% (VA-FI > 0.20–0.30; n = 16); log-rank $\chi^2 = 45.10$, df = 2, $p < 0.001$.

Is the Combined Model a Significant Improvement?

Using ACCI ≥ 5 for high comorbidity and VA-FI > 0.10 for elevated frailty, mortality was 15.1% (75/497) when neither index was elevated, 32.0% (48/150) with elevated VA-FI only, 60.0% (12/20) with elevated ACCI only, and 50.0% (19/38) with both (Fig. 4). Frailty therefore identified a subgroup with about twice the mortality among the 647 patients with ACCI < 5 (32.0% vs. 15.1%; Fisher exact $p < 0.001$). Among the 58 patients with ACCI ≥ 5, mortality was high irrespective of frailty (60.0% without and 50.0% with elevated VA-FI), and the combined "both" category (50.0%) was not higher than that of ACCI ≥ 5 overall (53.4%, 31/58); these groups were too small to draw conclusions about the added value of frailty at high ACCI. Nested likelihood-ratio tests indicated that adding VA-FI to an ACCI-only model significantly improved model fit ($\chi^2 = 10.55$, df = 1, $p = 0.0012$), and that adding ACCI to a VA-FI-only model produced a larger improvement ($\chi^2 = 34.43$, df = 1, $p < 0.001$). Adding age to a VA-FI-only model also significantly improved fit ($\chi^2 = 29.71$, df = 1, $p < 0.001$), and adding age to the combined ACCI + VA-FI model produced a further significant improvement ($\chi^2 = 9.50$, df = 1, $p = 0.0021$), suggesting that the age component of the ACCI does not fully capture the age gradient in this cohort. Because age alone and ACCI + VA-FI are non-nested predictor sets, we compared their fit using AIC (702.4 vs. 667.7, favoring ACCI + VA-FI) and the bootstrapped AUC difference (0.093; 95% CI, 0.049–0.143; $p < 0.001$), both favoring the combined model (Table 4). The combined model's AUC gain over ACCI alone was small and borderline statistically significant (0.016; 95% CI, 0.004 to 0.034; $p = 0.044$).

Table 4
Likelihood-ratio tests for nested model comparisons; AIC and bootstrapped AUC difference for the non-nested comparison against age alone.

Comparison	Test	Statistic	df	p-value
ACCI + VA-FI vs. ACCI alone	LR χ^2	10.55	1	0.0012
ACCI + VA-FI vs. VA-FI alone	LR χ^2	34.43	1	< 0.001
VA-FI + age vs. VA-FI alone	LR χ^2	29.71	1	< 0.001
ACCI + VA-FI + age vs. ACCI + VA-FI	LR χ^2	9.50	1	0.0021
ACCI + VA-FI vs. age alone	AIC / bootstrap AUC	ΔAIC = 34.7 / ΔAUC = 0.093 (0.049–0.143)	—	< 0.001
ACCI + VA-FI vs. ACCI alone	Bootstrap ΔAUC	0.016 (0.004–0.034)	---	0.044

Discussion

In this retrospective cohort of 705 screening colonoscopies followed for up to 13.5 years, 154 veterans died (21.8%), of whom 130 (18.4%) died within 10 years. The deceased patients had higher ACCI (median 3 vs 2) and higher VA-FI (median 0.10 vs 0.06). Older age is associated with higher mortality, and the relationship rises steadily across age groups. Mortality rose steadily from 5.0% in those under 50 to 50.0% in those aged 70–79 (75.0% of the four patients aged 80 or older). In the univariate Cox model, each step up in age group was associated with about a 2-fold higher hazard of death (HR 2.05, 95% CI 1.66–2.52). Mortality also rose with comorbidity (10.7% for ACCI 0–2 vs 53.4% for ACCI ≥ 5) and with frailty (16.8%, 33.1% and 62.5% across VA-FI categories). Preventive screening studies have shown that older age and/or multiple comorbidities predict death and that continued screening would not be beneficial. [20, 21]. The most commonly used comorbidity tool, the ACCI, can identify comorbidities; however, it cannot measure an individual's overall physiological reserve and vulnerability, functional status and independence, or cognitive and mental health status. Multiple large-scale studies in both older and younger populations have documented the negative impact of frailty on all-cause mortality, cardiovascular mortality, hospital admission, ICU stays, and post-procedural complications compared with non-frail populations. [4, 5, 12–14, 22, 23] Frailty predicted better acute adverse event outcomes during and immediately after colonoscopy in older adults than age and ACCI. [5] In our study, using the VA-FI, which is composed of 31 health deficits, the presence of frailty by the protocol threshold (VA-FI > 0.10) was associated with a 2.74-fold increase in unadjusted odds of death (35.6% vs 16.8%; Fisher exact $p < 0.001$), and each 0.10 increase in VA-FI carried about 2.5 times the hazard of death (univariate HR 2.47, 95% CI 1.91–3.21). Ten-year survival fell from 86.1% to 72.1% to 37.5% across VA-FI categories (the highest category included only 16 patients).

Comorbidity and frailty are related but not synonymous; they often overlap in older adults but can also occur in younger populations. The study found that the two indices (ACCI and VA-FI) were only moderately correlated (Spearman $\rho = 0.50$, Pearson $r = 0.472$; $p < 0.001$), indicating they are related but not interchangeable. Each remained independently associated with mortality after adjusting for the other. Frailty adds prognostic information that the age-comorbidity score alone does not capture; adding VA-FI to ACCI significantly improved model fit ($p = 0.0012$) and modestly improved discrimination (AUC 0.721 to 0.737; absolute gain 0.016, 95% CI 0.004 to 0.034), supporting its complementary prognostic value. Combining the indices also stratified risk. Mortality was 15.1% with neither flag (ACCI ≥ 5 or VA-FI > 0.10), 32.0% with elevated VA-FI only, 60.0% with elevated ACCI only (n = 20), and 50.0% with both (n = 38). The added value of frailty was clearest among the 647 patients with ACCI < 5, in whom an elevated VA-FI approximately doubled mortality (32.0% vs. 15.1%); among the 58 patients with ACCI ≥ 5, mortality was already high regardless of frailty, although the sample size was too small for firm conclusions.

The findings matter because current guidelines recommend that providers weigh life expectancy when deciding on screening and surveillance, yet offer little guidance on how to do so. A simple two-index approach could make that judgment more consistent. It could also help identify patients with limited life expectancy who are at risk of overuse, as well as younger patients whose burden of illness exceeds their age. That second group is relevant given the rising prevalence of chronic conditions and increasing

frailty among adults under 65. [6–8] Because screening benefits take years to accrue [24], a patient with a high combined risk may benefit less; however, this study did not measure screening benefit.

The study has several strengths. First, it included a long follow-up of up to 13.5 years, extending beyond the 10-year horizon relevant to decisions about screening and surveillance colonoscopy. Second, the outcome was all-cause mortality, an objective endpoint not subject to misclassification, and 154 deaths provided sufficient events to support multivariable modeling. Third, ACCI and VA-FI were calculated at the time of the index colonoscopy, so exposure was measured before the outcome occurred, preserving temporality despite the retrospective design. Fourth, we deliberately omitted a separate age term from the adjusted models to avoid double-counting age, which is already embedded in the ACCI. We also directly compared VA-FI plus age with ACCI. Fifth, the findings were consistent across complementary analytic approaches, including logistic regression, Cox proportional hazards, Kaplan-Meier analysis, likelihood-ratio test, and information criteria. Finally, VA-FI can be derived from routinely collected health record data, supporting the practical feasibility of combining it with ACCI to inform individualized decisions about colonoscopy.

Several limitations should be considered when interpreting and applying our recommendations in practice. First, this was a single-center retrospective study in a predominantly male population, limiting generalizability. Second, the study measured mortality, not the benefit or harm of colonoscopy. Nearly all examinations were normal (689 of 705), with very few polyps or abnormal findings and none with colorectal cancer, so we cannot determine which patients would have benefited. The proportion with adenomas (1.8%) was also lower than expected for screening populations, which may reflect how findings were recorded. Third, the AUC gain from adding VA-FI to ACCI was small, and overall discrimination was modest (AUC 0.74). These indices should inform, not replace, clinical judgment; shared decision-making between provider and patient should be used. Fourth, performance estimates were derived from the same cohort without external validation (10-fold cross-validated AUCs were similar: ACCI 0.71, VA-FI 0.67, ACCI + VA-FI 0.73), and the risk cutoffs (ACCI ≥ 5, VA-FI > 0.10) were not prospectively defined; the groups with elevated ACCI were small (n = 20 and 38). Lastly, the highest frailty group (VA-FI > 0.20) was small (n = 16), with no patients scoring > 0.30, and few were aged 80 or older (n = 4); these groups are often the most difficult for screening decisions.

In conclusion, comorbidity (ACCI) and frailty (VA-FI) were complementary predictors of long-term mortality among veterans undergoing screening colonoscopy. Adding VA-FI to ACCI significantly improved model fit and modestly improved discrimination (AUC from 0.721 to 0.737), with its main value in identifying higher-risk patients among those with ACCI < 5. Prospective, externally validated studies linking these indices to colonoscopy outcomes are needed before using them to determine who should be screened.

Declarations

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans for this research. No funding, in whole or in part, for this research.

- The authors did not receive support from any organization for the submitted work.
- No funding was received to assist with the preparation of this manuscript.
- No funding was received for conducting this study.
- No funds, grants, or other support was received.

US Federal copyright statement: The United States Department of Veterans Affairs (VA) places legal restrictions on access to veterans' health care data, including identifying data and sensitive patient information. The analytic data sets used in this study cannot leave the VA firewall without a Data Use Agreement. This limitation is consistent with that of other studies based on VA data. However, VA data are freely available to researchers behind the VA firewall under an approved VA study protocol. For more information, please visit https://www.virec.research.va.gov or contact the VA Information Resource Center (VIReC) at Virec@Va.gov.

Ethical approval human/animal statement: This is a retrospective study approved by the Miami VA Healthcare System Human Studies Subcommittee (IRBNet ID 1903927). All study personnel have been approved by the committee. A HIPAA Waiver was approved for this study. The Waiver of Authorization has been granted under 21 CFR 164.512(i)(1)(i)(A) – "Waiver of Authorization for Uses and Disclosures for Research Purposes approved by an IRB" on October 21st, 2025. Human Ethics and Consent to Participate declaration: Not applicable

Clinical trial number: Not applicable.

Author Contribution

A.S and M.Sh.- conceptualize the study, write the manuscript.M.S.,A.M.,I.D., G.C.,L.T. - data collection, edit and revise the manuscriptF.C. - administrative, stats.

Acknowledgement

n/a

References

1. Patel SG, May FP, Anderson JC, Burke CA, Dominitz JA, Gross SA, Jacobson BC, Shaukat A, Robertson DJ. Updates on Age to Start and Stop Colorectal Cancer Screening: Recommendations From the U.S. Multi-Society Task Force on Colorectal Cancer. Gastroenterology. 2022;162(1):285–299. doi: 10.1053/j.gastro.2021.10.007. Epub 2021 Nov 15.

2. El Halabi J, Burke CA, Hariri E, Rizk M, Macaron C, McMichael J, Rothberg MB. Frequency of Use and Outcomes of Colonoscopy in Individuals Older Than 75 Years. JAMA Intern Med. 2023;183(6):513–519. doi: 10.1001/jamainternmed.2023.0435.
3. Kahi CJ, Azzouz F, Juliar BE, Imperiale TF. Survival of elderly persons undergoing colonoscopy: implications for colorectal cancer screening and surveillance. Gastrointest Endosc. 2007;66(3):544–50. doi: 10.1016/j.gie.2007.01.008.
4. Toosizadeh N, Ehsani H, Taleban S, Golden T, Tirambulo C, Mohler J. Screening Colonoscopy Adverse Events in Aging Adults: Does Frailty Matter? J Geriatr Med Gerontol. 2018, 4:055. Doi: 10.23927/2469-5858/1510055.
5. Taleban S, Toosizadeh N, Junna S, Golden T, Ghazala S, Wadeea R, Tirambulo C, Mohler J. Frailty Assessment Predicts Acute Outcomes in Patients Undergoing Screening Colonoscopy. Dig Dis Sci. 2018;63(12):3272–3280. doi: 10.1007/s10620-018-5129-x. Epub 2018 May 24
6. Watson KB, Wiltz JL, Nhim K, Kaufmann RB, Thomas CW, Greenlund KJ. Trends in Multiple Chronic Conditions Among US Adults, By Life Stage, Behavioral Risk Factor Surveillance System, 2013–2023. Prev Chronic Dis. 2025;22:E15. doi: 10.5888/pcd22.240539.
7. Bai G, Wang Y, Mak JKL, Ericsson M, Hägg S, Jylhävä J. Is Frailty Different in Younger Adults Compared to Old? Prevalence, Characteristics, and Risk Factors of Early-Life and Late-Life Frailty in Samples from Sweden and UK. Gerontology. 2023;69(12):1385–1393. doi: 10.1159/000534131. Epub 2023 Sep 28.
8. Blodgett JM, Rockwood K, Theou O. Changes in the severity and lethality of age-related health deficit accumulation in the USA between 1999 and 2018: a population-based cohort study. Lancet Healthy Longev. 2021;2(2):e96-e104. doi: 10.1016/S2666-7568(20)30059-3. Epub 2021 Feb 3.
9. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–83. doi: 10.1016/0021-9681(87)90171-8.
10. Cho H, Klabunde CN, Yabroff KR, Wang Z, Meekins A, Lansdorp-Vogelaar I, Mariotto AB. Comorbidity-adjusted life expectancy: a new tool to inform recommendations for optimal screening strategies. Ann Intern Med. 2013;159(10):667–76. doi: 10.7326/0003-4819-159-10-201311190-00005.
11. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol. 1994;47(11):1245–1251. doi: 10.1016/0895-4356(94)90129-5.
12. Diaz-Toro F, Nazar G, Troncoso C, Concha-Cisternas Y, Leiva-Ordoñez AM, Martinez-Sanguinetti MA, Parra-Soto S, Lasserre-Laso N, Cigarroa I, Mardones L, Vásquez-Gómez J, Petermann-Rocha F, Diaz-Martinez X, Celis-Morales C; ELHOC Research Consortium. Frailty Index as a Predictor of Mortality in Middle-Aged and Older People: A Prospective Analysis of Chilean Adults. Int J Environ Res Public Health. 2023;20(2):1195. doi: 10.3390/ijerph20021195.
13. Kojima G, Iliffe S, Walters K. Frailty index as a predictor of mortality: a systematic review and meta-analysis. Age Ageing. 2018;47(2):193–200. doi: 10.1093/ageing/afx162.

14. Morales DR, Guthrie B, Downes TJ, McAllister DA, Hanlon P. Applicability of the electronic frailty index in younger and older adults in England: a population-based cohort study. Lancet Healthy Longev. 2025;6(8):100752. doi: 10.1016/j.lanhl.2025.100752. Epub 2025 Aug 21.
15. Orkaby AR, Nussbaum L, Ho YL, Gagnon D, Quach L, Ward R, Quaden R, Yaksic E, Harrington K, Paik JM, Kim DH, Wilson PW, Gaziano JM, Djousse L, Cho K, Driver JA. The Burden of Frailty Among U.S. Veterans and Its Association With Mortality, 2002–2012. J Gerontol A Biol Sci Med Sci. 2019;74(8):1257–1264. doi: 10.1093/gerona/gly232.
16. George EI, Hall DE, Youk A, Chen R, Kashikar A, Trickey AW, Varley PR, Shireman PK, Shinall MC Jr., Massarweh N, Johanning J, Aruya S. Association between patient frailty and postoperative mortality across multiple noncardiac surgical specialties. JAMA Surg. 2021;156(1):e205152. Epub 2021 Jan 13.
17. Shinall MC Jr, Arya S, Youk A, Varley P, Shah R, Massarweh NN, Shireman PK, Johanning JM, Brown AJ, Christie NA, Crist L, Curtin CM, Drolet BC, Dhupar R, Griffin J, Ibinson JW, Johnson JT, Kinney S, LaGrange C, Langerman A, Loyd GE, Mady LJ, Mott MP, Patri M, Siebler JC, Stimson CJ, Thorell WE, Vincent SA, Hall DE. Association of Preoperative Patient Frailty and Operative Stress With Postoperative Mortality. JAMA Surg. 2020;155(1):e194620. doi: 10.1001/jamasurg.2019.4620. Epub 2020 Jan 15.
18. La J, Lee MH, Brophy MT, Do NV, Driver JA, Tuck DP, Fillmore NR, Dumontier C. Baseline correlates of frailty and its association with survival in United States veterans with acute myeloid leukemia. Leuk Lymphoma. 2023;64(13):2081–2090. doi: 10.1080/10428194.2023.2254434. Epub 2023 Sep 6.
19. Cheng D, DuMontier C, Yildirim C, Charest B, Hawley CE, Zhuo M, Paik JM, Yaksic E, Gaziano JM, Do N, Brophy M, Cho K, Kim DH, Driver JA, Fillmore NR, Orkaby AR. Updating and Validating the U.S. Veterans Affairs Frailty Index: Transitioning From ICD-9 to ICD-10. J Gerontol A Biol Sci Med Sci. 2021;76(7):1318–1325. doi: 10.1093/gerona/glab071.
20. Demb J, Abraham L, Miglioretti DL, Sprague BL, O'Meara ES, Advani S, Henderson LM, Onega T, Buist DSM, Schousboe JT, Walter LC, Kerlikowske K, Braithwaite D; Breast Cancer Surveillance Consortium. Screening Mammography Outcomes: Risk of Breast Cancer and Mortality by Comorbidity Score and Age. J Natl Cancer Inst. 2020;112(6):599–606. doi: 10.1093/jnci/djz172.
21. Westerhout SF, Remmers S, Bangma CH, van Leenders GJLH, van Leeuwen PJ, Roobol MJ; ERSPC Rotterdam Study Group. Prostate cancer mortality among men with and without comorbidity: Long-term results from the European randomized study of screening for prostate cancer Rotterdam. Eur J Cancer. 2026;240:116741. doi: 10.1016/j.ejca.2026.116741. Epub 2026 Apr 12.
22. Qazi S, Seligman B, Preis SR, Rane M, Djousse L, Gagnon DR, Wilson PWF, Gaziano JM, Driver JA MD, MPH, Cho K, Orkaby AR; Million Veteran Program (MVP). Measuring Frailty Using Self-Report or Automated Tools to Identify Risk of Cardiovascular Events and Mortality: The Million Veteran Program. J Am Heart Assoc. 2024;13(16):e033111. doi: 10.1161/JAHA.123.033111. Epub 2024 Aug 19.

23. De Geer L, Fredrikson M, Chew MS. Frailty is a stronger predictor of death in younger intensive care patients than in older patients: a prospective observational study. Ann Intensive Care. 2022;12(1):120. doi: 10.1186/s13613-022-01098-2.
24. Kaminski MF, Kalager M, Løberg M, Emilsson L, Macios A, Samy F, Shi J, Fielding S, Hernán MA, Garborg K, Rupinski M, Dekker E, Spaander M, Holme Ø, Zauber AG, Pilonis ND, Didkowska J, Spychalski P, Hoff G, Regula J, Adami HO, Bretthauer M; NordICC Study Group*. Long-term effects of colonoscopy screening on colorectal cancer incidence and mortality: a multicountry, population-based randomised controlled trial. Lancet. 2026;407(10541):1787–1795. doi: 10.1016/S0140-6736(26)00508-8. Epub 2026 May 5.

Figures

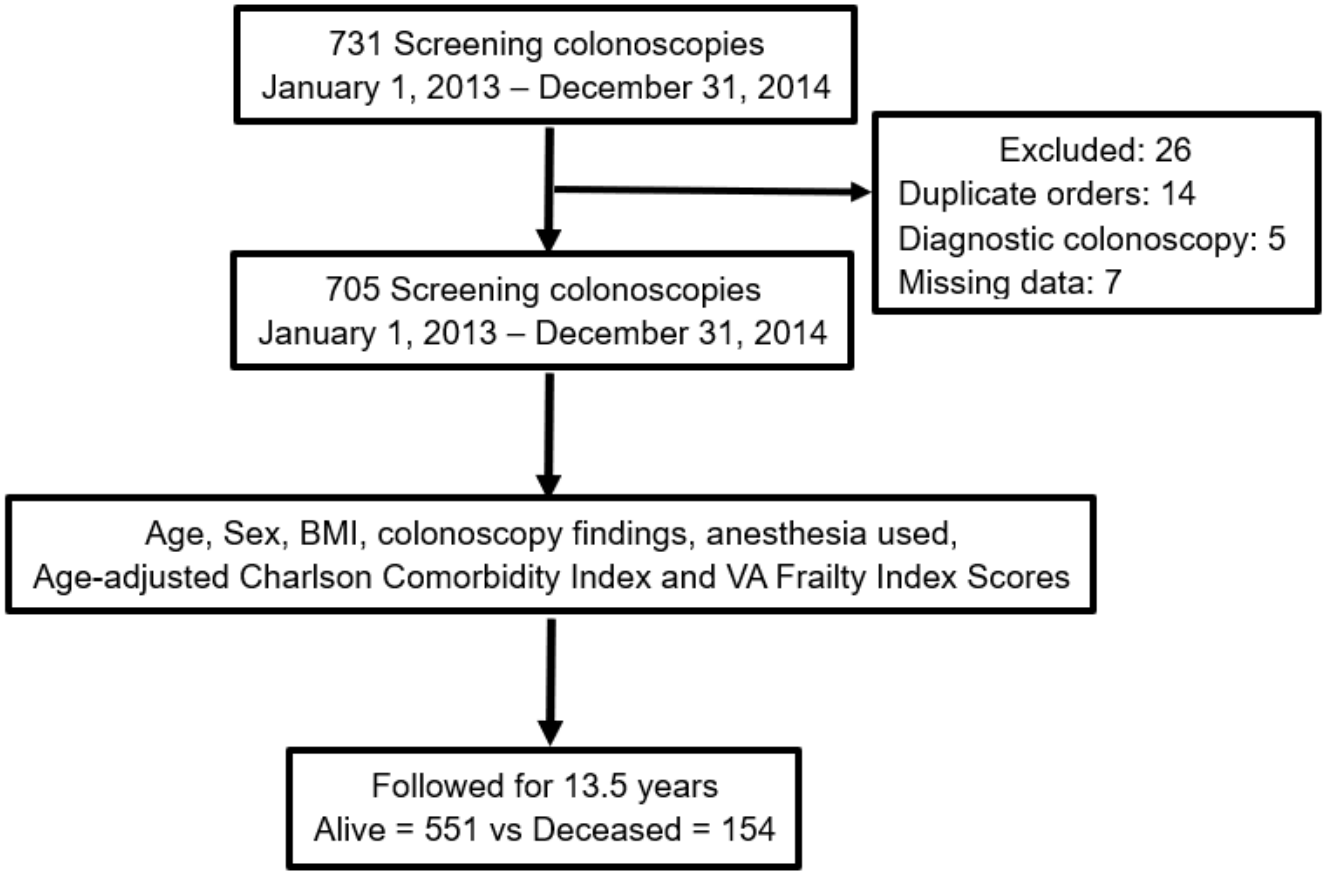

Figure 1

Flow Diagram

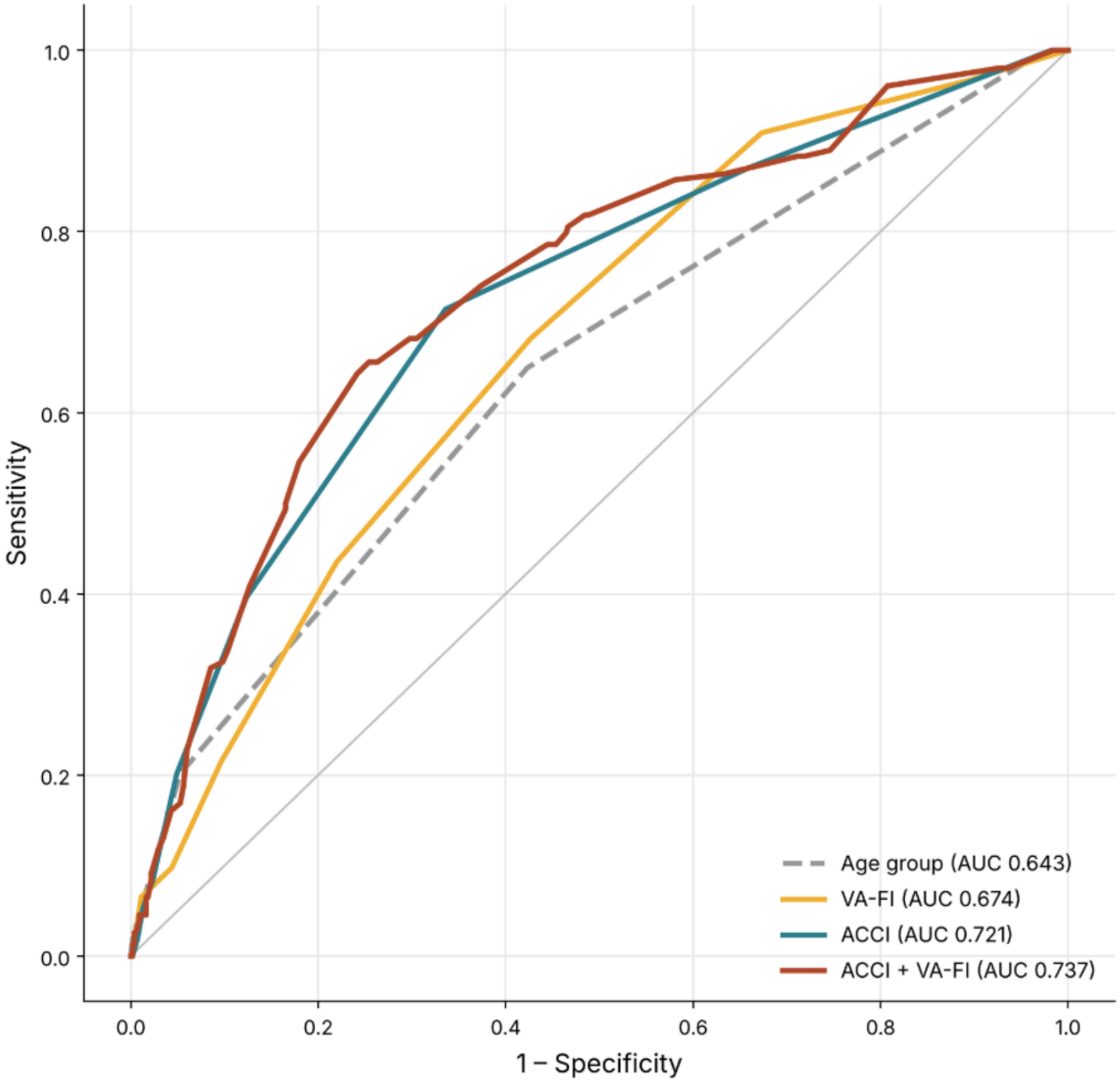

Figure 2

Receiver operating characteristic curves for prediction of mortality (age group, VA-FI, ACCI, and ACCI + VA-FI).

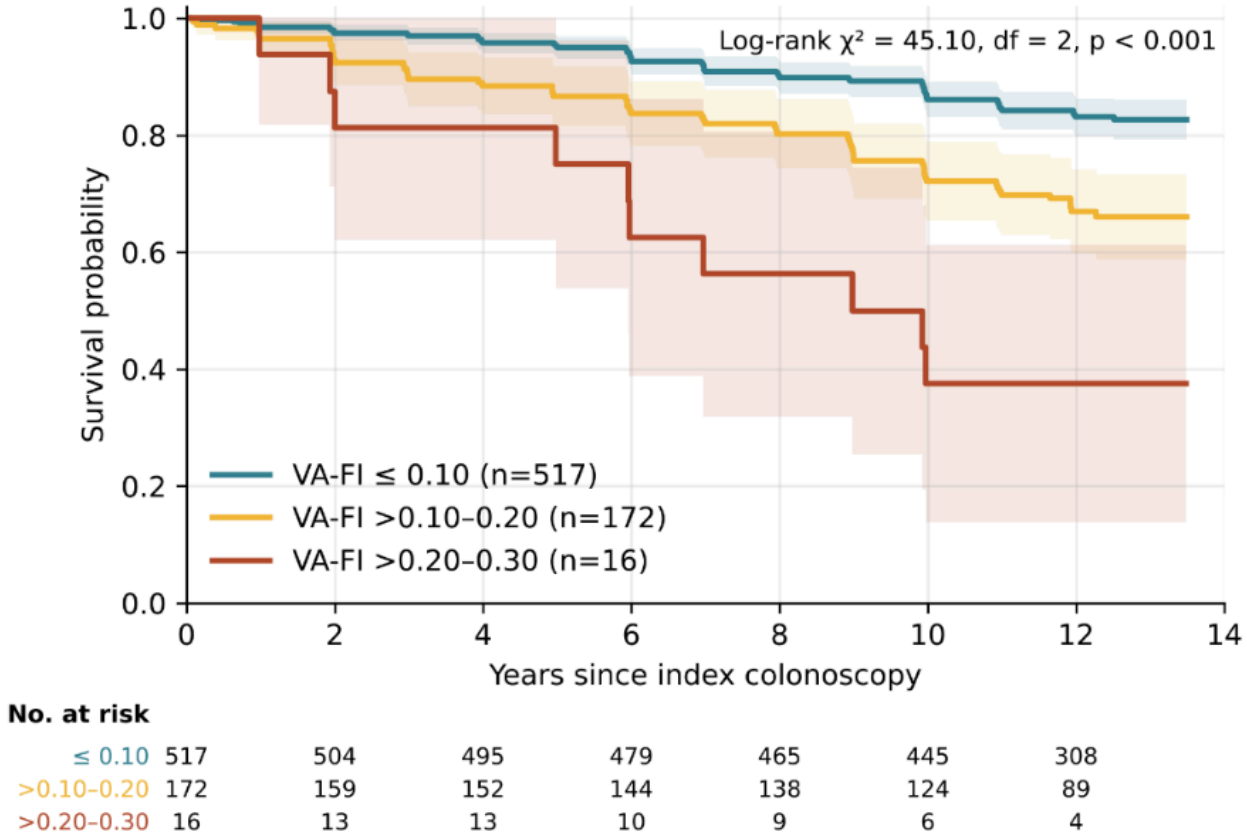

Figure 3

Kaplan-Meier survival curves according to the VA Frailty Index (shaded bands, 95% confidence intervals; numbers at risk shown below the plot).

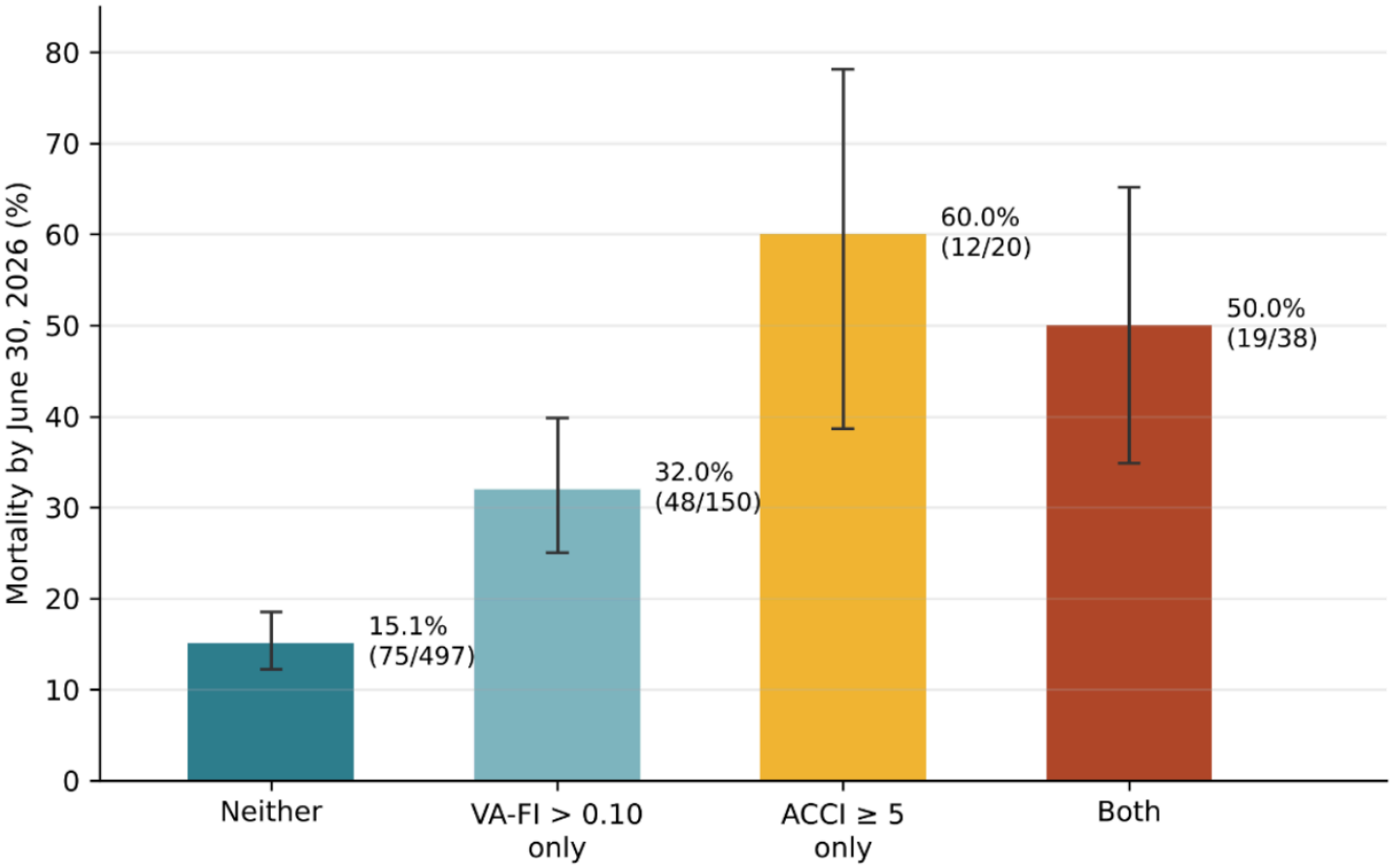

Figure 4

Mortality according to combined ACCI ≥ 5 and VA-FI > 0.10 status (error bars, 95% Wilson confidence intervals).