

Beyond Chronological Age: Comorbidity Burden and Physiological Reserve Determine Survival After a Positive Screening Fecal Occult Blood Test in Older Adults

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Abstract

Background

Colorectal cancer (CRC) screening guidelines recommend individualized decision-making after age 75 years. However, evidence supporting health-based colonoscopy triage in Asian settings is limited. This study aimed to evaluate colonoscopy yield and 5-year survival after a positive fecal occult blood test (FOBT) in older Thai adults.

Methods

A retrospective cohort study was conducted in consecutive patients aged ≥ 75 years who underwent FOBT-based CRC screening at a Thai university hospital between 2012 and 2019. The primary endpoints were the diagnostic yield of screening colonoscopy (CRC and advanced adenoma detection) and 5-year all-cause mortality. Survival probabilities were estimated using Kaplan–Meier analyses. Mortality predictors were determined using Cox proportional hazards models supported by competing-risk and propensity-score analyses. To account for potential immortal-time bias, a landmark analysis was performed.

Results

Among 709 older adults with positive screening FOBT (mean age 80.9 years), 162 (22.8%) underwent colonoscopy. Clinically significant lesions were identified in 51.2% of patients (CRC 23.5%; advanced adenoma 27.8%), with no observed procedure-related complications (95% CI, 0.0%–2.3%). The estimated 5-year overall survival was 70.4%, strongly stratified by Charlson Comorbidity Index (CCI) (85.9% for CCI 3–4 vs. 50.1% for CCI ≥ 7 ; $p < 0.001$). Independent mortality predictors included end-stage renal disease (aHR 2.14, 95% CI 1.22–3.76), coronary artery disease (aHR 1.88, 95% CI 1.11–3.20), and serum albumin (aHR 0.43 per g/dL increase, 95% CI 0.32–0.58). Competing-risk analysis showed non-cancer death (26.0%) was 7.2-fold more common than CRC death (3.6%).

Conclusions

Comorbidity burden and physiological reserve, rather than chronological age, primarily determine survival after a positive FOBT. Screening policies in older populations should incorporate multidimensional comorbidity and physiological assessments to optimize colonoscopy utilization and prevent over-screening.

Introduction

Colorectal cancer (CRC) is a leading cause of cancer-related mortality worldwide [1]. In Thailand, the shift towards an aging society has led to a steady rise in CRC incidence over the past two decades. CRC is currently the third most common malignancy in men, the fourth most common in women and its incidence increases significantly with age [2, 3]. Approximately 70% of sporadic CRCs develop from adenomatous polyps through the adenoma–carcinoma sequence over 10 to 15 years. The identification and removal of these precursor lesions can prevent cancer and lower mortality [4–6].

Because early CRC and its precursors are typically asymptomatic, routine screening for average-risk adults is widely recommended, generally starting at age 45 or 50 years [7–12]. However, the decision to continue screening in older adults requires an individualized approach. The U.S. Preventive Services Task Force recommends that routine screening be performed in any adult until at the age of 75 years and suggests that screening for adults aged 76–85 years be based on overall health and prior screening history; the adults aged over 85 years are not recommended [7]. Similarly, the U.S. Multi-Society Task Force and the American College of Physicians suggest to stop screening when life expectancy falls below 10 years or after age 75 [8, 13, 14]. In Thailand, the National Cancer Institute clinical practice guideline recommends annual fecal occult blood tests (FOBT) for average-risk adults from age 50, with a positive result leading to a colonoscopy referral; this guideline does not specify an upper age limit [15].

In clinical practice, FOBT-based screening is still frequently performed in adults older than 75 years; nevertheless, it remains unclear whether all these patients receive a net clinical benefit [16, 17]. This creates a clinical dilemma in geriatric gastroenterology; however, the risk of CRC increases with age, declining life expectancy and a higher burden of competing comorbidities primarily determine overall survival [18, 19]. The procedural risks of colonoscopy and the physical toll of subsequent cancer treatments are more significant in frail older adults [18, 19]. Predictive modeling suggests that screening offers little benefit when life expectancy is less than 5 years [19–21]. Consequently, several researchers have proposed that any decision to stop screening should consider age, comorbidities, and screening history, rather than chronological age alone [17, 21].

While colonoscopy is highly accurate and allows for therapeutic polypectomy, it carries risks, and the impact of a positive FOBT extends beyond the procedure. False-positive results are common, and the subsequent colonoscopy carries risks of perforation, bleeding, and cardiopulmonary events, which affect older frail adults more severely [18, 22]. Evidence balancing these risks and benefits in older Asian populations is limited. Data on the clinical trajectory of older Thai adults after a positive FOBT—including colonoscopy uptake rates, diagnostic yields, and factors predicting long-term survival—are needed to guide context-specific recommendations for CRC screening in Thailand.

This study primarily aimed to evaluate the diagnostic yield—specifically the detection rates of CRC and advanced adenomas—derived from FOBT-based screening in adults aged ≥ 75 years old, and to determine the 5-year overall survival rate after a positive screening result. Secondary objectives included assessing procedure- and treatment-related complications, identifying clinical predictors of mortality, and evaluating the proportion of deaths caused by CRC versus competing conditions.

Methods

Study design and setting

A retrospective cohort study was conducted at Siriraj Hospital, a 2,200-bed tertiary university medical center affiliated with the Faculty of Medicine Siriraj Hospital, Mahidol University, in Bangkok, Thailand. The study protocol was approved by the Siriraj Institutional Review Board (Si722/2024), which waived the requirement for informed consent due to the retrospective observational nature of the investigation. All patient records were de-identified and managed on a secure, restricted-access database. The study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines [23].

Study Population and Selection Criteria

Consecutive patients aged ≥ 75 years who had a documented positive FOBT during routine CRC screening at the General Medicine and Geriatric outpatient clinics between January 1, 2012, and December 31, 2019, were identified. The index screening test comprised either a conventional guaiac-based FOBT (gFOBT) or a fecal immunochemical test (FIT), reflecting the institutional transition during the study period. Exclusion criteria were: (i) FOBT performed for diagnostic evaluation of overt gastrointestinal symptoms (e.g., unexplained iron-deficiency anemia, overt rectal bleeding, unintentional weight loss, or persistent bowel habit changes) rather than routine screening; (ii) a documented personal history of CRC, previous colorectal resection, or known colorectal polyps; and (iii) missing essential baseline clinical records. Referrals for diagnostic colonoscopy following positive FOBT results were managed individually according to attending physician judgment, shared decision-making with patients and families, and underlying clinical fitness.

Variables and Data Collection

Demographic and clinical data, including age, sex, body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), and comorbid conditions based on the Charlson Comorbidity Index (CCI; calculated without age adjustment), were extracted from electronic health records. Baseline laboratory measurements obtained within 3 months of the index positive FOBT—including hemoglobin, hematocrit, white blood cell count, blood urea nitrogen, serum creatinine, and serum albumin—were recorded. Details regarding colonoscopy completion, endoscopic findings, histopathology, procedural complications, and cancer-directed therapies were systematically documented. Vital status and verified cause of death were determined via linkage with institutional electronic records and the Thai National Civil Registration database. Implausible anthropometric entries (BMI < 12 or > 45 kg/m²; $n = 5$) were coded as missing data.

Study Outcomes and Definitions

In concordance with international consensus guidelines, an advanced adenoma was defined by the presence of at least one of the following: maximum polyp diameter ≥ 10 mm, three or more discrete adenomas, or high-grade dysplasia/villous histopathology [9]. Clinically significant colorectal lesions were defined as confirmed invasive CRC or advanced adenoma. Colonoscopy-related complications encompassed intestinal perforation, post-procedural bleeding, hemodynamic instability, hypoxemia, aspiration pneumonia, and severe electrolyte/metabolic disturbances attributable to bowel preparation. Cancer treatment-related complications included major operative morbidity or treatment-limiting chemotherapy toxicities.

The primary endpoints were the diagnostic yield of colonoscopy (detection rates of CRC and advanced adenomas) and 5-year all-cause survival calculated from the date of the index positive FOBT. Secondary endpoints included complication rates from endoscopy and cancer treatment, independent clinical predictors of 5-year mortality, and cause-specific cumulative incidence of death (CRC mortality vs. competing non-cancer causes).

Sample Size Calculation

The sample size was estimated a priori. Based on an anticipated 15% absolute difference in 5-year survival between patients undergoing colonoscopy versus those managed without endoscopy, a minimum sample size of 708 patients was required to achieve 90% statistical power at a two-sided alpha level of 0.05 (nQuery, Statistical Solutions Ltd, Cork, Ireland). All 709 consecutive eligible patients identified during the observation period were included in the analytic cohort.

Statistical analysis

Continuous variables were summarized as mean $\pm$ standard deviations (SD) or medians with interquartile ranges (IQRs). Categorical variables were reported as frequencies and percentages. Comparisons between groups were made using the Mann–Whitney U test for continuous data and the χ^2 or Fisher's exact test for categorical data. The 5-year overall survival probability was estimated using the Kaplan–Meier method.

Data extraction and analysis were conducted exclusively after institutional review board approval was granted on September 17, 2024. To strictly comply with institutional guidelines for retrospective research, which mandate that all analyzed events must predate the approval date, the study observation window was predefined to end prior to IRB approval. Consequently, the database was locked and all follow-up was administratively censored on September 10, 2024. No patient information or events occurring after this date were accessed or included. Ninety-five percent confidence intervals (CIs) were computed using Greenwood's formula. Survival distributions were compared with the logarithmic rank test, and median follow-up was calculated using the reverse Kaplan–Meier method.

Independent predictors of 5-year mortality were evaluated using Cox proportional hazards regression. Variables with a univariate p-value < 0.10 or established biological relevance were included in the multivariable model. Serum albumin and hemoglobin were analysed as continuous variables. The proportional hazards assumption was checked using Schoenfeld residuals, and model discrimination was measured with Harrell's concordance index (c-index). To account for potential immortal-time bias, a landmark analysis was performed by excluding patients who died or were censored within the first 3 months and re-assessing the association between colonoscopy and survival from that landmark. Pre-specified sensitivity analyses were conducted to account for potential healthy user selection bias regarding who received a colonoscopy, including progressive covariate adjustment and propensity-score methods. Cause-specific mortality was analysed using competing-risk methods (Aalen–Johansen cumulative incidence functions and cause-specific hazard models). A two-sided p-value < 0.05 indicated statistical significance. The analyses were performed using SPSS Statistics version 28.0 (IBM Corp., Armonk, NY, USA).

Results

Cohort characteristics

Between January 2012 and December 2019, 2,102 patients aged ≥ 75 years underwent FOBT screening, of whom 709 (33.7%) had a positive test result and constituted the primary analytic cohort (Fig. 1). Guaiac-based FOBT was the index test in 604 patients (85.2%) and FIT in 105 patients (14.8%). The mean age was 80.9 ± 4.8 years (range 75–107 years), with 330 patients (46.5%) older than 80 years; 388 (54.7%) were female. Multimorbidity was highly prevalent, with 637 patients (89.8%) having at least one chronic underlying condition. Common diagnoses included hypertension (73.9%), chronic kidney disease (49.5%, including 9.4% with end-stage renal disease [ESRD]), diabetes mellitus (35.8%), and coronary artery disease (18.3%). The mean unadjusted CCI was 5.4 ± 1.9 (39.2% CCI 3–4, 33.6% CCI 5–6, and 27.2% CCI ≥ 7). Among the 308 patients with recorded anthropometric measurements, the mean BMI was 22.6 ± 4.9 kg/m², and 15.2% were classified as underweight (BMI < 18.5 kg/m²) by Asian-specific criteria. Median hemoglobin was 10.0 g/dL (IQR 8.7–11.4; mean 10.1 ± 2.0 g/dL) and median serum albumin was 3.3 g/dL (IQR 2.8–3.8; mean 3.22 ± 0.74 g/dL) (Table 1).

Table 1

Baseline characteristics of FOBT-positive patients aged ≥ 75 years at Siriraj Hospital, stratified by 5-year survival status (N = 709)

Characteristic	Total cohort (n = 709)	Survivors (n = 564)	Deceased (n = 145)	p-value
Demographics				
Age, years, mean $\pm$ SD	80.9 $\pm$ 4.8	80.7 $\pm$ 4.3	81.8 $\pm$ 5.5	0.032
Age > 80 years, n (%)	330 (46.5)	253 (45.0)	77 (52.4)	0.110
Female sex, n (%)	388 (54.7)	307 (54.6)	81 (55.1)	0.918
BMI, kg/m ² (n = 308)	22.6 $\pm$ 4.9	22.7 $\pm$ 4.6	22.0 $\pm$ 5.9	0.341
Comorbidities, n (%)				
Any underlying disease	637 (89.8)	493 (87.7)	144 (98.0)	< 0.001
Hypertension	524 (73.9)	413 (73.5)	111 (75.5)	0.616
Diabetes (any type)	254 (35.8)	194 (34.5)	60 (40.8)	0.155
Diabetes with complications	157 (22.1)	115 (20.5)	42 (28.6)	0.035
Dyslipidemia	319 (45.0)	256 (45.6)	63 (42.9)	0.560
Cerebrovascular disease	130 (18.3)	94 (16.7)	36 (24.5)	0.030
Dementia	48 (6.8)	34 (6.0)	14 (9.5)	0.130
CKD any stage	351 (49.5)	267 (47.5)	84 (57.1)	0.040
End-stage renal disease	67 (9.4)	44 (7.8)	23 (15.6)	0.004
Coronary artery disease	130 (18.3)	89 (15.8)	41 (27.9)	0.001
Congestive heart failure	16 (2.3)	9 (1.6)	7 (4.8)	0.029
Liver disease	37 (5.2)	21 (3.7)	16 (10.9)	0.001
Solid tumor (any)	53 (7.5)	36 (6.4)	17 (11.6)	0.034
Charlson Comorbidity Index (CCI)				
CCI, mean $\pm$ SD	5.4 $\pm$ 1.9	5.2 $\pm$ 1.8	6.6 $\pm$ 2.1	< 0.001
CCI 3–4, n (%)	278 (39.2)	250 (44.5)	28 (19.0)	< 0.001
CCI 5–6, n (%)	238 (33.6)	184 (32.7)	54 (36.7)	
Continuous variables are presented as mean $\pm$ standard deviation or median with interquartile range [IQR]; categorical variables as n (%). Between-group comparisons used Student's t-test or Mann–Whitney U test for continuous variables and Chi-square test or Fisher's exact test for categorical variables. BMI, body mass index; CCI, Charlson Comorbidity Index; CKD, chronic kidney disease; FOBT, fecal occult blood test; SD, standard deviation.				

Characteristic	Total cohort (n = 709)	Survivors (n = 564)	Deceased (n = 145)	p-value
Demographics				
CCI ≥ 7 , n (%)	193 (27.2)	128 (22.8)	65 (44.2)	
Laboratory values				
Hemoglobin, g/dL (n = 680), mean $\pm$ SD [median, IQR]	10.1 $\pm$ 2.0 [10.0, 8.7– 11.4]	10.2 $\pm$ 2.1 [10.2, 8.9–11.6]	9.6 $\pm$ 1.7 [9.5, 8.4–10.8]	< 0.001
Hematocrit, % (n = 681), mean $\pm$ SD	31.1 $\pm$ 6.0	31.6 $\pm$ 6.2	29.3 $\pm$ 5.0	< 0.001
Albumin, g/dL (n = 412), mean $\pm$ SD [median, IQR]	3.22 $\pm$ 0.74 [3.3, 2.8–3.8]	3.32 $\pm$ 0.72 [3.4, 2.9–3.9]	2.88 $\pm$ 0.73 [2.9, 2.4–3.4]	< 0.001
Creatinine, mg/dL (n = 672), mean $\pm$ SD	1.62 $\pm$ 1.66	1.59 $\pm$ 1.62	1.74 $\pm$ 1.81	0.323
Continuous variables are presented as mean $\pm$ standard deviation or median with interquartile range [IQR]; categorical variables as n (%). Between-group comparisons used Student's t-test or Mann–Whitney U test for continuous variables and Chi-square test or Fisher's exact test for categorical variables. BMI, body mass index; CCI, Charlson Comorbidity Index; CKD, chronic kidney disease; FOBT, fecal occult blood test; SD, standard deviation.				

Colonoscopy uptake and diagnostic yield

Colonoscopy was performed in 162 of the 709 FOBT-positive patients (22.8%). Uptake was lower among patients aged > 80 years (19.7% vs. 25.6% in the 75–80 age group), those with a higher comorbidity burden (17.6% in CCI ≥ 7 vs. 29.9% in CCI 3–4), and those with a history of cerebrovascular disease (13.8%). Compared with the non-scoped group, patients who underwent colonoscopy were younger (79.7 vs. 81.3 years, $p < 0.001$), had a lower mean CCI (4.9 vs. 5.6, $p < 0.001$), and had higher mean hemoglobin levels (10.2 vs. 9.8 g/dL, $p = 0.033$).

In the scoped cohort, CRC was identified endoscopically in 38 patients (23.5%). Three additional cases were diagnosed via alternative methods (imaging or surgical biopsy), bringing the total to 41 CRC diagnoses (5.8% of the cohort). Advanced adenomas were found in 45 patients (27.8%), meaning a clinically significant lesion was detected in 83 of the 162 scoped patients (51.2%). No colonoscopy-related complications (perforation, hemorrhage, hypotension, hypoxemia, aspiration, or bowel-preparation-related events) were recorded (0/162; 95% exact binomial CI, 0.0%–2.3%). The detection rate of significant lesions was similar between patients aged 75–80 and those > 80 years (53.6% vs. 47.7%) and across CCI strata (51.8%, 53.3%, and 47.1% for CCI 3–4, 5–6, and ≥ 7 , respectively) (Table 2).

Table 2

Benefits and burdens of FOBT-based colorectal cancer screening: colonoscopy yield, complications, and cancer treatment outcomes

Outcome	n / N	Rate (%)
Screening pathway		
FOBT-positive among those screened	709 / 2,102	33.7
Colonoscopy completion after positive FOBT	162 / 709	22.8
Colonoscopy findings (n = 162)		
Colorectal cancer	38 / 162	23.5
Advanced adenoma (CRC excluded)	45 / 162	27.8
Any clinically significant lesion	83 / 162	51.2
Non-advanced adenoma only	1 / 162	0.6
Diverticulosis	26 / 162	16.0
Hemorrhoids	28 / 162	17.3
Benign ulcer	6 / 162	3.7
Normal endoscopy	42 / 162	25.9
Procedural safety		
Colonoscopy-related complications	0 / 162	0.0
CRC management and outcomes		
Total CRC diagnosed (all modalities)	41 / 709	5.8
Cancer-directed treatment among CRC	27 / 41	65.9
Treatment-related complications	2 / 41	4.9
All-cause mortality among CRC	7 / 41	17.1
Cancer-attributable mortality among CRC	3 / 41	7.3
Yield by age stratum (n = 162 scoped)		
CRC + advanced adenoma – age 75–80 yr	52 / 97	53.6
CRC + advanced adenoma – age > 80 yr	31 / 65	47.7
Yield by Charlson Comorbidity Index		
CRC + advanced adenoma – CCI 3–4	43 / 83	51.8
Advanced adenoma was defined as any polyp ≥ 10 mm in maximum dimension, ≥ 3 polyps, or villous architecture. CCI, Charlson Comorbidity Index; CRC, colorectal cancer; FOBT, fecal occult blood test.		

Outcome	n / N	Rate (%)
Screening pathway		
CRC + advanced adenoma — CCI 5–6	24 / 45	53.3
CRC + advanced adenoma — CCI ≥ 7	16 / 34	47.1
Advanced adenoma was defined as any polyp ≥ 10 mm in maximum dimension, ≥ 3 polyps, or villous architecture. CCI, Charlson Comorbidity Index; CRC, colorectal cancer; FOBT, fecal occult blood test.		

Management and outcomes of detected colorectal cancer

Among the 41 patients diagnosed with CRC, 27 (65.9%) received cancer-directed therapy (surgical resection, $n = 25$; systemic chemotherapy, $n = 2$). Patients receiving active cancer treatment had comparable baseline age (80.1 vs. 81.0 years) and CCI scores (4.4 vs. 4.9) to those managed conservatively. Treatment-related complications occurred in 2 of 41 patients (4.9%). During follow-up, 7 of the 41 CRC patients died (all-cause mortality 17.1%); however, only 3 deaths were directly attributable to CRC progression (cancer-specific mortality 7.3%).

Survival and predictors of mortality

The median follow-up time (reverse Kaplan-Meier method) was 2.5 years (IQR 1.0–5.0), and 145 patients (20.5%) died. The estimated 1-, 2-, and 5-year overall survival probabilities for the entire cohort were 85.3%, 80.1%, and 70.4% (95% CI 65.9–74.5%), respectively.

Overall survival showed clear differences based on the burden of comorbidity: 5-year survival was 85.9% (95% CI 79.8–90.3%) for patients with a CCI of 3–4, 67.2% (58.9–74.2%) for a CCI of 5–6, and 50.1% (40.1–59.3%) for a CCI ≥ 7 (log-rank $p < 0.001$) (Fig. 2B). In contrast, chronological age provided a smaller difference in prognosis: 74.3% (68.2–79.4%) for patients ≤ 80 years compared to 66.1% (59.1–72.1%) for those > 80 years (log-rank $p = 0.061$). Patients who had a colonoscopy showed a higher unadjusted 5-year survival than patients who did not undergo colonoscopy (76.9% vs. 68.3%; log-rank $p = 0.025$) (Fig. 2A), but this difference was reduced after multivariable adjustment, indicating selection bias (Table 3).

Table 3

Estimated 5-year overall survival from Kaplan–Meier analysis, stratified by clinical subgroups

Subgroup	N	Deaths	5-yr survival, % (95% CI)	Log-rank p-value
Overall cohort				
All FOBT-positive patients	709	145	70.4 (65.9–74.5)	—
By chronological age				
Age 75–80 years	379	67	74.3 (68.2–79.4)	0.061
Age > 80 years	330	78	66.1 (59.1–72.1)	
By colonoscopy uptake				
Colonoscopy performed	162	27	76.9 (67.8–83.7)	0.025
Colonoscopy not performed	547	118	68.3 (62.9–73.1)	
By Charlson Comorbidity Index				
CCI 3–4	278	27	85.9 (79.8–90.3)	< 0.001
CCI 5–6	238	54	67.2 (58.9–74.2)	
CCI ≥ 7	193	64	50.1 (40.1–59.3)	
By CRC diagnosis				
CRC diagnosed	41	7	74.8 (53.3–87.4)	0.563
No CRC	668	138	70.1 (65.5–74.3)	
Survival times were censored at 5 years. P-values are from log-rank tests for the full stratification. CCI, Charlson Comorbidity Index; CI, confidence interval; CRC, colorectal cancer; FOBT, fecal occult blood test. A total of 145 deaths occurred within the 5-year follow-up window used for Kaplan-Meier analysis.				

The multivariable Cox analysis (Table 4 and Fig. 3) included 409 patients (three patients from the 412 with albumin data were excluded due to missing values in other covariates). To assess potential selection bias from missing albumin data, patients with (n = 412) and without (n = 297) available albumin were compared: the two groups were similar in age (81.1 vs. 80.7 years, p = 0.245), colonoscopy uptake (23.1% vs. 22.6%, p = 0.948), and mortality (22.3% vs. 18.5%, p = 0.254), although those with albumin data had a marginally higher comorbidity burden (mean CCI 5.6 vs. 5.2, p = 0.039), consistent with sicker patients being more likely to have albumin measured. The model identified three independent predictors of 5-year mortality: end-stage renal disease (adjusted hazard ratio [aHR] 2.14, 95% CI 1.22–3.76; p = 0.008), coronary artery disease (aHR 1.88, 1.11–3.20; p = 0.019) and serum albumin levels (aHR 0.43 per g/dL increase, 0.32–0.58; p < 0.001). Liver disease had a borderline association with mortality (aHR 2.00, 0.99–4.01; p = 0.052). After adjustment, chronological age, sex, hemoglobin levels, CRC detection, and

undergoing a colonoscopy did not remain independent predictors of survival. The multivariable model showed good discrimination (Harrell's c-index 0.74).

Table 4
Univariable and multivariable Cox proportional hazards models for 5-year all-cause mortality

Variable	Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Age (per year)	1.04 (1.01–1.07)	0.021	1.01 (0.97–1.05)	0.546
Male sex	0.97 (0.70–1.35)	0.859	—	—
Diabetes with complications	1.54 (1.08–2.21)	0.018	0.65 (0.37–1.14)	0.136
Cerebrovascular disease	1.56 (1.06–2.28)	0.022	1.10 (0.64–1.90)	0.724
End-stage renal disease	2.71 (1.73–4.24)	< 0.001	2.14 (1.22–3.76)	0.008
Coronary artery disease	1.78 (1.23–2.56)	0.002	1.88 (1.11–3.20)	0.019
Congestive heart failure	2.74 (1.28–5.88)	0.009	—	—
Liver disease (any)	2.64 (1.52–4.58)	0.001	2.00 (0.99–4.01)	0.052
CCI (per point increase)	1.34 (1.24–1.45)	< 0.001	—	—
Hemoglobin (per g/dL)	0.83 (0.76–0.90)	< 0.001	0.98 (0.86–1.12)	0.801
Albumin (per g/dL)	0.42 (0.32–0.55)	< 0.001	0.43 (0.32–0.58)	< 0.001
Colonoscopy performed	0.62 (0.41–0.95)	0.026	0.66 (0.37–1.20)	0.175
Colorectal cancer detected	0.74 (0.35–1.58)	0.435	1.10 (0.36–3.41)	0.867
Multivariable model included age, diabetes with complications, cerebrovascular disease, end-stage renal disease, coronary artery disease, liver disease, hemoglobin, albumin, colonoscopy performance, and colorectal cancer detection. The analysis was based on 409 patients with complete data, including 91 deaths. *CCI was excluded from the multivariable model due to collinearity with its individual component diseases. Variables not entered into the multivariable model are indicated by '—'. The c-index of the multivariable model was 0.74. CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio.				

These results were supported by sensitivity analyses (Tables S1–S3). The unadjusted survival advantage associated with colonoscopy (HR 0.62, 95% CI 0.41–0.95) was reduced after progressive adjustment for age, comorbidity, and physiological reserve (fully adjusted HR 0.66, 95% CI 0.37–1.20; $p = 0.175$). A landmark analysis excluding patients who died or were censored within the first 3 months (leaving 546 patients) yielded a concordant, non-significant association between colonoscopy and survival (log-rank $p = 0.399$; adjusted HR 1.08, 95% CI 0.58–2.02), further indicating that the apparent benefit reflected healthy-user selection rather than a protective effect of the procedure. Multiple-imputation estimates for missing data matched the complete-case model. Calculated E-values quantified the minimum strength

of unmeasured confounding required to explain the observed associations (4.08 for albumin and 3.70 for end-stage renal disease).

Competing risk analyses showed that non-cancer mortality was the primary risk (Fig. 4). The 5-year cumulative incidence of non-cancer death was 26.0%, compared with 3.6% for CRC-related death, representing a 7.2-fold difference. This gap increased in patients with more comorbidities: the 5-year cumulative incidence of non-cancer death rose from 13.1% in patients with a CCI of 3–4 to 28.2% for a CCI of 5–6, and to 43.6% for a CCI ≥ 7 . Cancer-related deaths remained low across these groups (1.0%, 4.6%, and 6.2%, respectively). In cause-specific hazard models, lower serum albumin (cause-specific hazard ratio 0.45 per g/dL, 0.33–0.60) and end-stage renal disease (2.15, 1.17–3.94) independently predicted non-cancer mortality. This confirms that competing comorbid illnesses, rather than the detected cancer, were the main threat to survival.

Discussion

In this cohort of 709 older Thai adults with positive FOBT, three primary observations provide context for CRC screening policy. First, comorbidity burden and physiological reserve appear to have a more substantial influence on 5-year survival than chronological age. Second, colonoscopy demonstrated a high yield of clinically significant lesions in all age and CCI strata. Third, only a minority of eligible patients (22.8%) underwent colonoscopy and most subsequent deaths (87.1%) were not related to CRC. These findings suggest that rigid, age-based screening cutoffs may not be optimal, and support an individualized approach to endoscopic triage that considers overall health.

The association between CCI and survival—ranging from an 86% five-year survival rate for patients with a CCI of 3–4 to 50% for those with a CCI ≥ 7 —is consistent with data from Western cohorts [17, 19, 21]. These findings align with modeling studies indicating that patients with a life expectancy of under five years may derive less net benefit from screening [18]. The observation that comorbidity has a stronger association with survival than chronological age in the multivariable model aligns with long-term outcome data in older adults following a positive FOBT, as well as population data regarding the potential harms of over-screening [24]. Furthermore, the association between serum albumin (aHR 0.43 per g/dL) and survival warrants attention. Rather than a marker of nutritional status alone, serum albumin is a negative acute-phase reactant that reflects systemic inflammation, illness burden, and diminished physiological reserve, and it correlates with clinical frailty [25–28]. This suggests that standard laboratory markers may assist in tailoring endoscopic triage for geriatric populations.

The detection rate of clinically significant lesions (consistently defined as colorectal cancer or advanced adenomas) was 51.2%, which matches the yields reported in Western geriatric screening programs [29–31]. However, this high diagnostic yield must be interpreted with caution. Because colonoscopy referrals were determined on a case-by-case basis, fitter patients who could tolerate the procedure were preferentially selected. This selection bias likely inflates the diagnostic yield compared to an unselected cohort of all FOBT-positive older adults. Nevertheless, it suggests that a positive FOBT remains a robust

indicator of pathology in older patients deemed fit for investigation. This finding underscores that the primary challenge is not the performance of the screening modality itself, but rather the effective identification of patients with the physiological reserve to undergo subsequent diagnostic procedures and potential cancer-directed therapies.

A key clinical question raised by these findings is how to appropriately select older adults for colonoscopy. The diagnostic yield was significant even in older and more comorbid groups: CRC or advanced adenoma was found in 47.7% of scoped patients aged > 80 years and 47.1% of those with a CCI ≥ 7 . There were no complications recorded in 162 endoscopies in this selected group (95% CI, 0.0%–2.3%), and only one cancer-related death occurred among the 27 CRC patients who underwent cancer-directed therapy. The clinical focus could shift from chronological age to physiological reserve and life expectancy, placing comprehensive geriatric assessment at the center of shared decision-making.

These results provide practical considerations for expanding CRC screening programs in Thailand and similar middle-income Asian countries [3]. Strict chronological age cut off points (often 50–75 years) are administratively simple but lack biological justification: a 75-year-old with a CCI of 3–4 has a 5-year survival rate similar to a healthy 65-year-old, while a peer with a CCI ≥ 7 faces a 50% risk of 5-year mortality. Policy refinements could include incorporating a comorbidity assessment (such as the CCI) along with markers of physiological reserve (such as serum albumin) into decisions regarding FOBT screening and colonoscopy in patients aged ≥ 75 years. Shared decision-making should discuss the trade-off between the diagnostic yield of colonoscopy and the risk of non-cancer mortality, framing the choice to stop screening as a goal-concordant medical practice rather than a withdrawal of care.

This study has several limitations. First, the unadjusted survival benefit observed with colonoscopy was reduced after multivariable adjustment, heavily pointing to healthy user selection. Due to the observational design and low procedure uptake (22.8%), substantial residual confounding and selection bias are present. We must explicitly emphasize that this study does not establish a causal effect of colonoscopy on long-term survival. Although propensity-score analyses supported these findings and calculated E-values quantified the potential impact of unmeasured confounding, residual bias cannot be entirely excluded. Second, although no procedure-related complications were recorded, this observation should be interpreted with caution. The low rate of uptake of colonoscopy suggests that clinicians may have selectively referred only the most physically robust patients, which may not reflect the risk of complications in a broader, unselected population. Third, serum albumin data was missing for 297 patients (41.9%), restricting the main multivariable model to 409 patients; however, multiple-imputation analyses on the full cohort produced consistent results. Fourth, the specific reasons for non-referral to colonoscopy were not consistently documented in the medical records, limiting the ability to analyse the determinants of procedure completion. Finally, the retrospective design prevented the analysis of functional status assessments, which are critical components of screening decisions in older adults.

Conclusion

In older Thai adults with a positive FOBT screening, subsequent colonoscopy demonstrated a high diagnostic yield for colorectal cancer and advanced adenomas across all age and comorbidity groups. However, 5-year overall survival was primarily determined by the burden of comorbidities—specifically end-stage renal disease and coronary artery disease—and physiological reserve (reflected by serum albumin), making chronological age an insufficient independent predictor. Because overall procedural uptake was low and most subsequent mortality was not caused by CRC, screening policies in aging populations may benefit from moving beyond strict chronological age cutoffs. Integrating brief comorbidity and physiological-reserve assessments can help identify older adults who have the physiological reserve to benefit from completing the screening pathway.

Declarations

Ethics approval and consent to participate

The study protocol was reviewed and approved by the Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University (Certificate of Approval Si722/2024). The requirement for informed consent was waived by the institutional review board due to the retrospective observational nature of the study. All procedures were performed in accordance with the ethical standards of the institutional research committee and the 1964 Declaration of Helsinki and its later amendments.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to institutional data protection policies but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

CC conceived the study, acquired and curated the clinical data, performed statistical analyses, and drafted the original manuscript. UK contributed to study conception and design, interpreted the endoscopic findings, and critically revised the manuscript for intellectual content. US conceptualized and supervised the study, contributed to methodological design and geriatric data interpretation, critically

revised the manuscript, and had final responsibility for the submission. All authors read and approved the final manuscript.

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References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*. 2021;71(3):209–49.
2. Lohsiriwat V, Chaisomboon N, Pattana-Arun J. Current Colorectal Cancer in Thailand. *Ann Coloproctol*. 2020;36(2):78–82.
3. Tiankanon K, Aniwat S, Rerknimitr R. Current Status of Colorectal Cancer and Its Public Health Burden in Thailand. *Clin Endosc*. 2021;54(4):499–504.
4. Kuipers EJ, Grady WM, Lieberman D, Seufferlein T, Sung JJ, Boelens PG, et al. Colorectal cancer. *Nat Rev Dis Primers*. 2015;1:15065.
5. Crockett SD, Nagtegaal ID, Terminology. Molecular Features, Epidemiology, and Management of Serrated Colorectal Neoplasia. *Gastroenterology*. 2019;157(4):949–e664.
6. Bresalier RS. Colorectal Cancer Screening in a Changing World. *Gastroenterol Clin North Am*. 2022;51(3):577–91.
7. Force UPST. Screening for Colorectal Cancer: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2021;325(19):1965–77.
8. Rex DK, Boland CR, Dominitz JA, Giardiello FM, Johnson DA, Kaltenbach T, et al. Colorectal Cancer Screening: Recommendations for Physicians and Patients from the U.S. Multi-Society Task Force on Colorectal Cancer. *Am J Gastroenterol*. 2017;112(7):1016–30.
9. Shaikat A, Kahi CJ, Burke CA, Rabeneck L, Sauer BG, Rex DK. ACG Clinical Guidelines: Colorectal Cancer Screening 2021. *Am J Gastroenterol*. 2021;116(3):458–79.
10. Jacobsson M, Wagner V, Kanneganti S. Screening for Colorectal Cancer. *Surg Clin North Am*. 2024;104(3):595–607.
11. Ladabaum U, Dominitz JA, Kahi C, Schoen RE. Strategies for Colorectal Cancer Screening. *Gastroenterology*. 2020;158(2):418–32.
12. Helsingen LM, Kalager M. Colorectal Cancer Screening - Approach, Evidence, and Future Directions. *NEJM Evid*. 2022;1(1):EVIDra2100035.
13. Qaseem A, Harrod CS, Crandall CJ, Wilt TJ, Balk EM, Cooney TG, et al. Screening for Colorectal Cancer in Asymptomatic Average-Risk Adults: A Guidance Statement From the American College of Physicians (Version 2). *Ann Intern Med*. 2023;176(8):1092–100.

14. Patel SG, May FP, Anderson JC, Burke CA, Dominitz JA, Gross SA, et al. 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):285–99.
15. Chaiweerawattana A, Kornlak A, Sukarayothin S, Khuhaprema T, editors. *Clinical Practice Guidelines for Colorectal Cancer Screening, Diagnosis and Treatment*. 1st ed. Bangkok: National Cancer Institute; 2009.
16. Arora A, Chadi SA, Chesney T. What Should We Recommend for Colorectal Cancer Screening in Adults Aged 75 and Older? *Curr Oncol*. 2021;28(4):2540–7.
17. Cenin DR, Tinmouth J, Naber SK, Dubé C, McCurdy BR, Paszat L, et al. Calculation of Stop Ages for Colorectal Cancer Screening Based on Comorbidities and Screening History. *Clin Gastroenterol Hepatol*. 2021;19(3):547–55.
18. Kistler CE, Kirby KA, Lee D, Casadei MA, Walter LC. Long-term outcomes following positive fecal occult blood test results in older adults: benefits and burdens. *Arch Intern Med*. 2011;171(15):1344–51.
19. Lee SJ, Boscardin WJ, Stijacic-Cenzer I, Conell-Price J, O'Brien S, Walter LC. Time lag to benefit after screening for breast and colorectal cancer: meta-analysis of survival data from the United States, Sweden, United Kingdom, and Denmark. *BMJ*. 2013;346:e8441.
20. van Hees F, Saini SD, Lansdorp-Vogelaar I, Vijan S, Meester RG, de Koning HJ, et al. Personalizing colonoscopy screening for elderly individuals based on screening history, cancer risk, and comorbidity status could increase cost effectiveness. *Gastroenterology*. 2015;149(6):1425–37.
21. Lansdorp-Vogelaar I, Gulati R, Mariotto AB, Schechter CB, de Carvalho TM, Knudsen AB, et al. Personalizing age of cancer screening cessation based on comorbid conditions: model estimates of harms and benefits. *Ann Intern Med*. 2014;161(2):104–12.
22. Day LW, Kwon A, Inadomi JM, Walter LC, Somsouk M. Adverse events in older patients undergoing colonoscopy: a systematic review and meta-analysis. *Gastrointest Endosc*. 2011;74(4):885–96.
23. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007;370(9596):1453–7.
24. Walter LC, Lindquist K, Nugent S, Schult T, Lee SJ, Casadei MA, et al. Impact of age and comorbidity on colorectal cancer screening among older veterans. *Ann Intern Med*. 2009;150(7):465–73.
25. Bonnefoy M, Berrut G, Lesourd B, Ferry M, Gilbert T, Guérin O, et al. Frailty and nutrition: searching for evidence. *J Nutr Health Aging*. 2015;19(3):250–7.
26. Cabrerizo S, Cuadras D, Gomez-Busto F, Artaza-Artabe I, Marín-Ciancas F, Malafarina V. Serum albumin and health in older people: Review and meta analysis. *Maturitas*. 2015;81(1):17–27.
27. Soysal P, Veronese N, Arik F, Kalan U, Smith L, Isik AT. Mini Nutritional Assessment Scale-Short Form can be useful for frailty screening in older adults. *Clin Interv Aging*. 2019;14:693–9.
28. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet*. 2013;381(9868):752–62.

29. Lin OS, Kozarek RA, Schembre DB, Ayub K, Gluck M, Drennan F, et al. Screening colonoscopy in very elderly patients: prevalence of neoplasia and estimated impact on life expectancy. JAMA. 2006;295(20):2357–65.
30. Ma W, Wang K, Nguyen LH, Joshi A, Cao Y, Nishihara R, et al. Association of Screening Lower Endoscopy With Colorectal Cancer Incidence and Mortality in Adults Older Than 75 Years. JAMA Oncol. 2021;7(7):985–92.
31. García-Albéniz X, Hsu J, Bretthauer M, Hernán MA. Effectiveness of Screening Colonoscopy to Prevent Colorectal Cancer Among Medicare Beneficiaries Aged 70 to 79 Years: A Prospective Observational Study. Ann Intern Med. 2017;166(1):18–26.

Figures

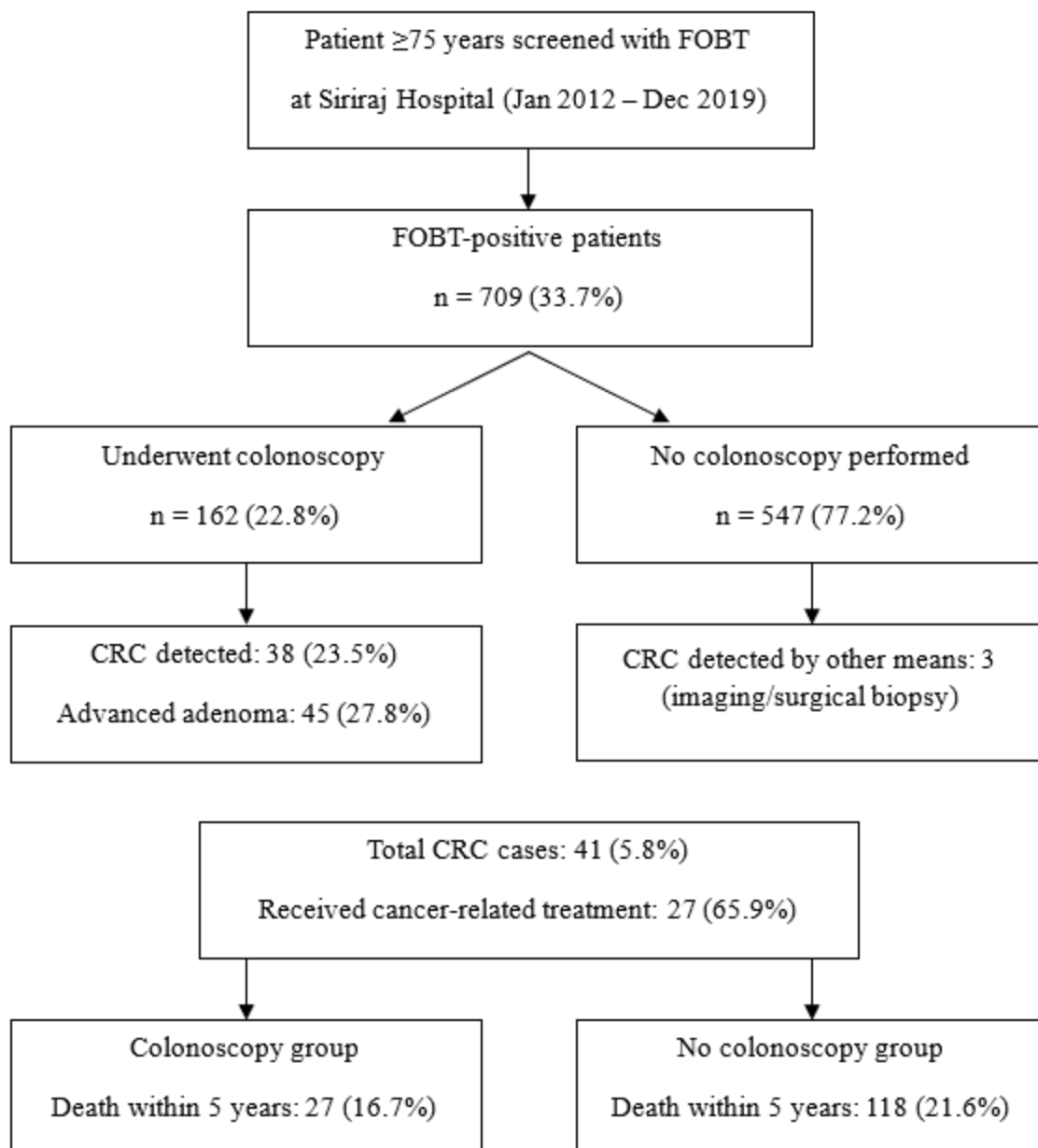


Figure 1

Patient flow through the study. Flow diagram delineating screening FOBT identification, colonoscopy triage, diagnostic yields of neoplastic lesions, and 5-year vital status stratification in older adults aged ≥ 75 years.

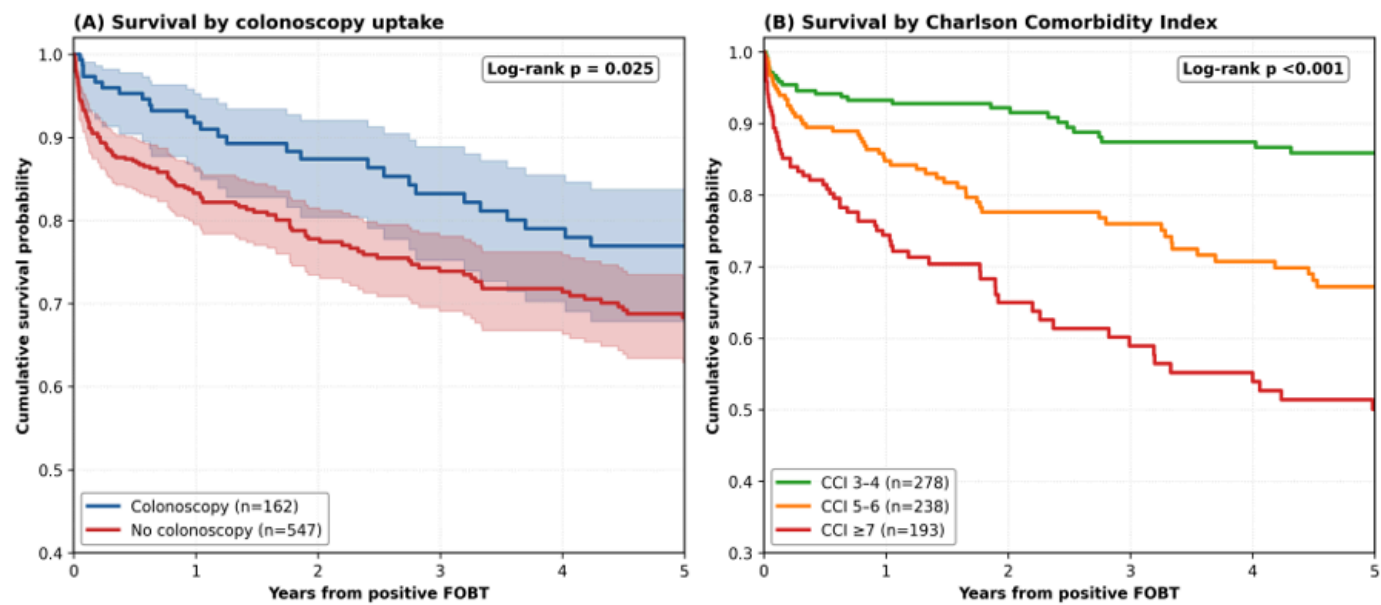


Figure 2

Kaplan–Meier estimates of 5-year overall survival. (A) Cumulative survival stratified by colonoscopy completion (log-rank $p = 0.025$; attenuated after multivariable adjustment). (B) Cumulative survival stratified by Charlson Comorbidity Index (CCI) categories: CCI 3–4 (green), CCI 5–6 (orange), and CCI ≥ 7 (red) (log-rank $p < 0.001$).

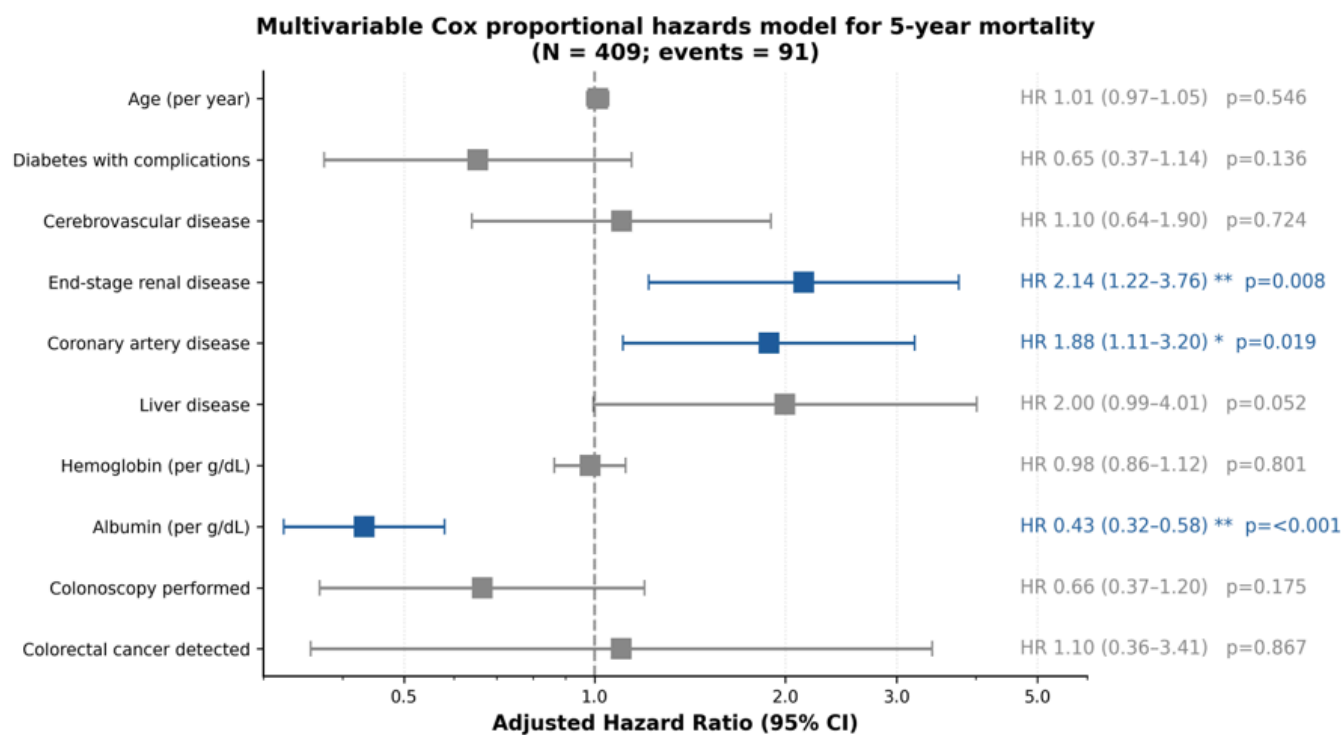


Figure 3

Forest plot of independent predictors of 5-year all-cause mortality. Multivariable Cox proportional hazards model (n = 409; 91 events). Squares indicate adjusted hazard ratios (aHR), and horizontal lines represent 95% confidence intervals. Statistically significant predictors (p < 0.05) are highlighted in blue.

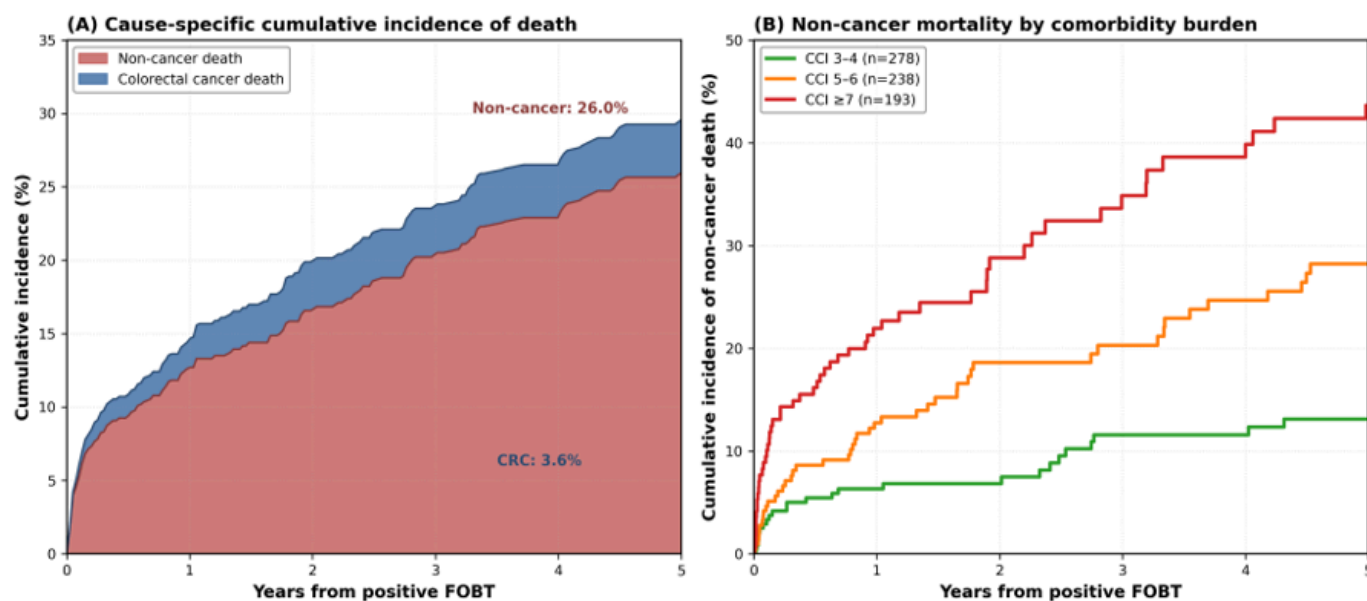


Figure 4

Competing-risk analysis of cause-specific mortality. (A) 5-year cumulative incidence of non-cancer death (26.0%) versus colorectal cancer-specific death (3.6%) in the overall cohort (7.2-fold higher risk for competing non-cancer causes). (B) Cumulative incidence of non-cancer death across Charlson Comorbidity Index tiers.

Supplementary Files

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