IBD Dialogues: Building Generations

IBD Across the Ages: Elderly

Alessandro Armuzzi
Milan, Italy

ECCO

EFCCA
European Federation of Crohn's & Ulcerative Colitis Associations

Disclosures

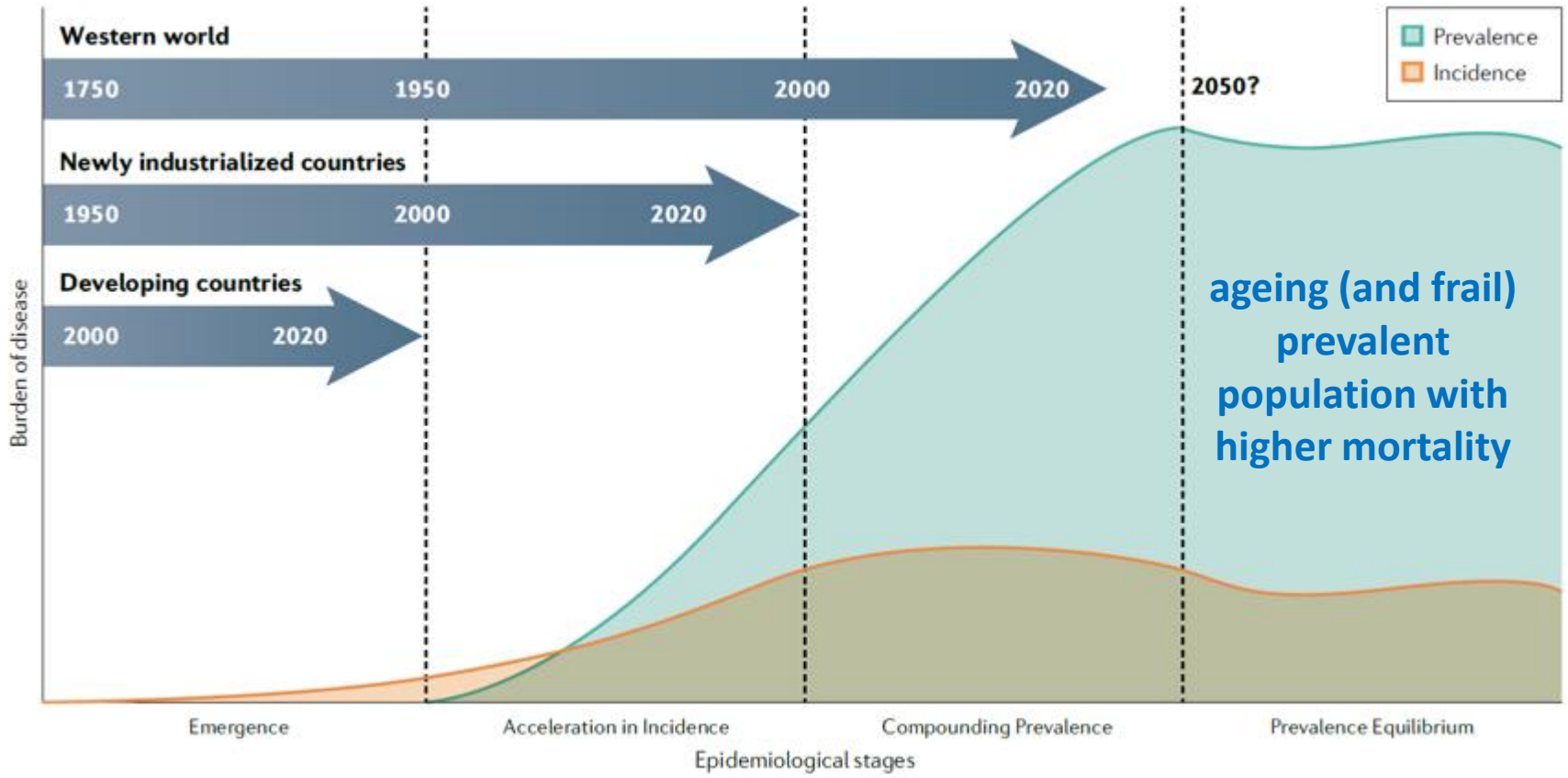
- Consulting/advisory board fees from AbbVie, Allergan, Amgen, Arena, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Celltrion, Eli-Lilly, Ferring, Galapagos, Gilead, Janssen, Lionhealth, MSD, Mylan, Nestlé ,Pfizer, Protagonist Therapeutics, Roche, Samsung Bioepis, Sandoz, Takeda, Tillots Pharma

- Speaker's fees from AbbVie, Amgen, Arena, Biogen, Bristol-Myers Squibb, Eli-Lilly, Ferring, Galapagos, Gilead, Janssen, Lionhealth, MSD, Novartis, Pfizer, Roche, Samsung Bioepis, Sandoz, Takeda, Teva Pharmaceuticals, Tigenix

- Research grants from MSD, Takeda, Pfizer, Biogen

The Four Epidemiological Stages In The Global Evolution Of IBD

IBD
1) Early onset (mostly)
2) Chronic
3) Low mortality



Adapted from Kaplan GG, Windsor JW. Nat Rev Gastroenterol Hepatol 2021

Who is an elderly IBD patient?

ECCO Topical Review

European Crohn's and Colitis Organisation Topical Review on IBD in the Elderly

ECCO Current Practice Position 1

The widely accepted definition of elderly-onset IBD is disease onset at an age of 60 years or older. When making management decisions in the elderly, clinicians should assess an individual's frailty, rather than only considering an individual's chronological/biological age

Fit elderly

Frail elderly

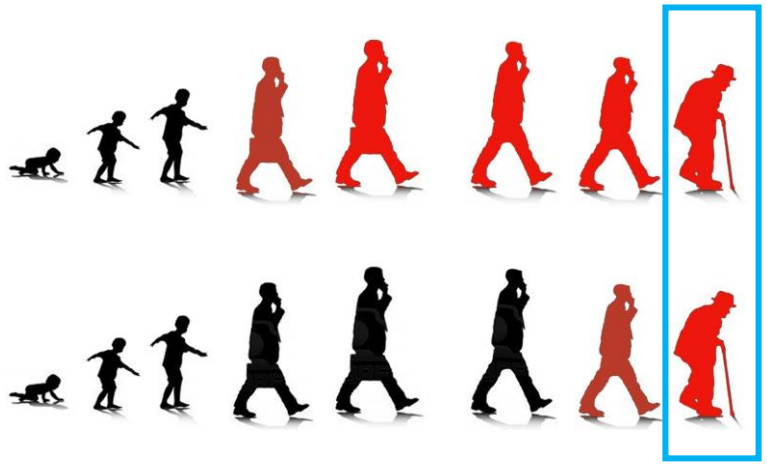
A very heterogeneous condition…

ECCO Topical Review; JCC 2017

IBD in the elderly (25%-35%): Two different conditions sharing common concerns

Elderly IBD patients with disease onset at a younger age (20%)

Elderly-onset IBD patients (15%)



Specific challenges

- Misdiagnoses challenge

- Different natural history of IBD

Common concerns

- Comorbidities issues

- Increased risk of side effects of medical and surgical treatments

ECCO Topical Review; JCC 2017

Misdiagnoses challenge

	Symptoms	Possible discrimination with IBD
Infectious gastroenteritis	Acute onset of diarrhoea	Recent antibiotic useStool sample for pathogenic organisms, including *C. difficile*
Ischaemic disease	Bloody diarrhoeaAcute abdominal pain, associated with meal intake	Thorough cardiovascular history taking [including congestive heart failure, cardiac arrhythmias, atherosclerotic disease, embolic disease, vasculitis and diabetes]Different localization pattern
Diverticular disease [diverticulitis]	Abdominal painDiarrhoea	History of diverticular disease Local inflammation around diverticular part of the colon during endoscopy
Microscopic colitis	Non-bloody diarrhoea Predominantly in females	No anatomical abnormalities visible at endoscopyHistologically different from IBD
NSAID-induced enteritis	Diarrhoea Abdominal pain	History of NSAID use
Radiation colitis	Bloody diarrhoea Abdominal pain	History of abdominal or pelvic radiation Histologically different from IBD
Rectal ulcer syndrome	Bloody diarrhoea	History of constipationHistologically different from IBD

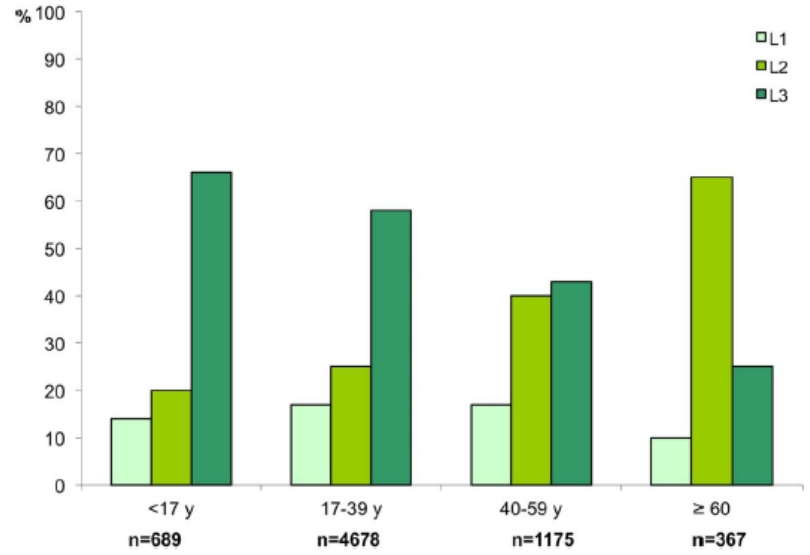
Diagnostic work-up in elderly IBD does not differ from other adult patients

ECCO Topical Review; JCC 2017

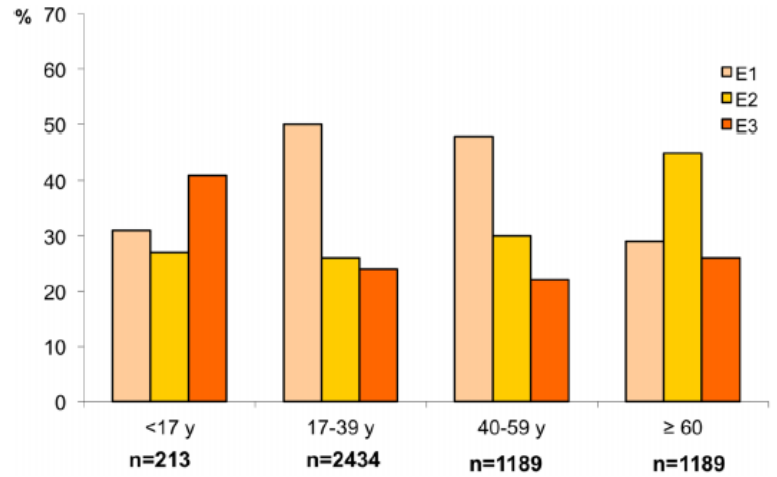
Different natural history of IBD

Location of disease

CD

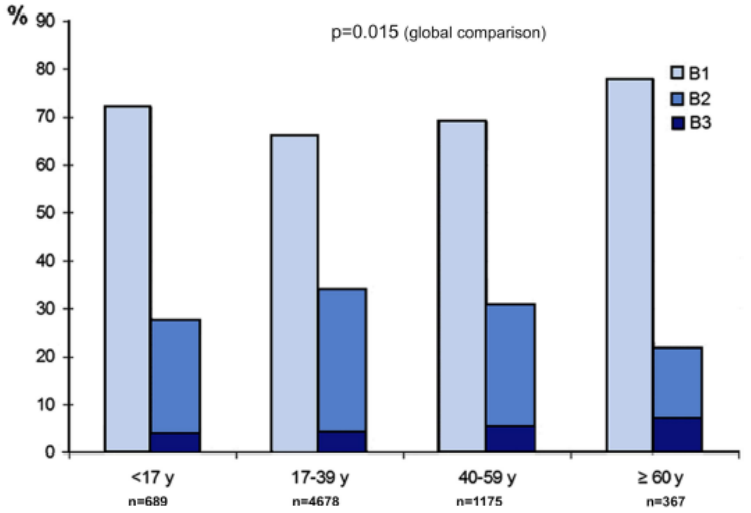


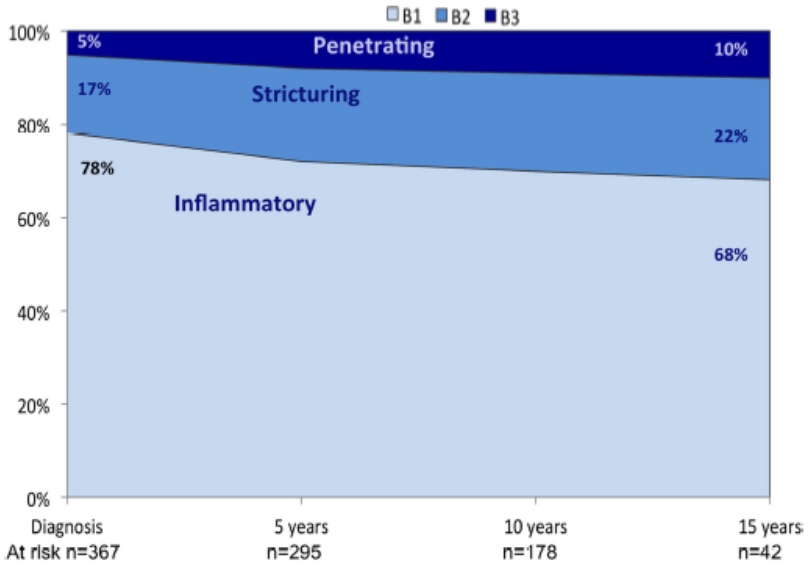
UC



Behaviour of disease

CD





Charpentier C, ey al. Gut 2014

Comorbidity: practical implications

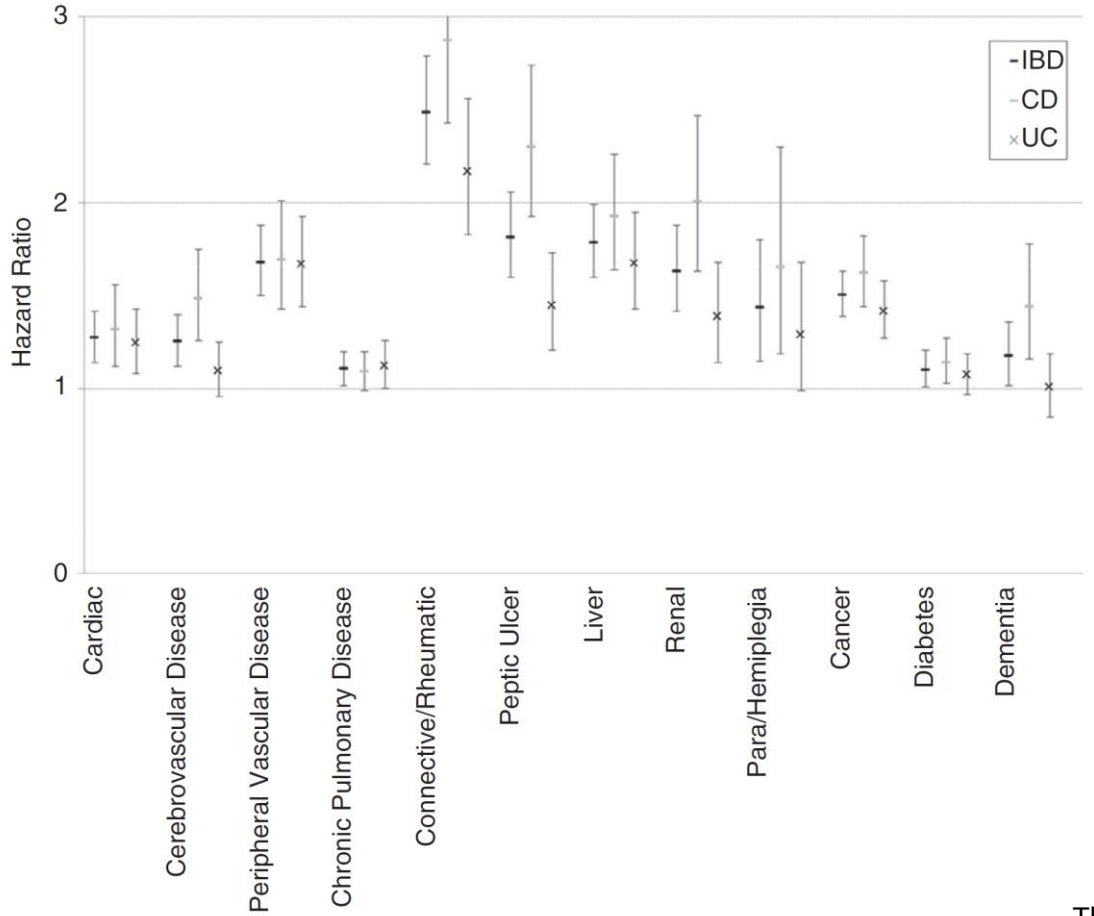
Comorbidity can significantly change several scenarios of medical practice in IBD:

1. Clinical manifestations of IBD can be altered or confused by associated diseases
2. Prognosis of IBD may be influenced
3. Whenever a patient with significant comorbidity is seen by physicians, they step outside the realm of medical evidence
4. The use of drugs for the treatment of IBD is limited by the increased importance their pharmacologic or collateral effects can have on a person with comorbid conditions
5. It is more important than ever to set up multidisciplinary team to empower patient care

De Groot V, et al. J Clin Epidemiol 2003; Lopez-Sanroman A, et al. WJG 2011

Comorbidities in IBD

Hazard ratios of comorbid diseases in IBD (n 9247) and Crohn's disease (n 4253) and ulcerative colitis (n 4994) compared to matched controls (n 85691)



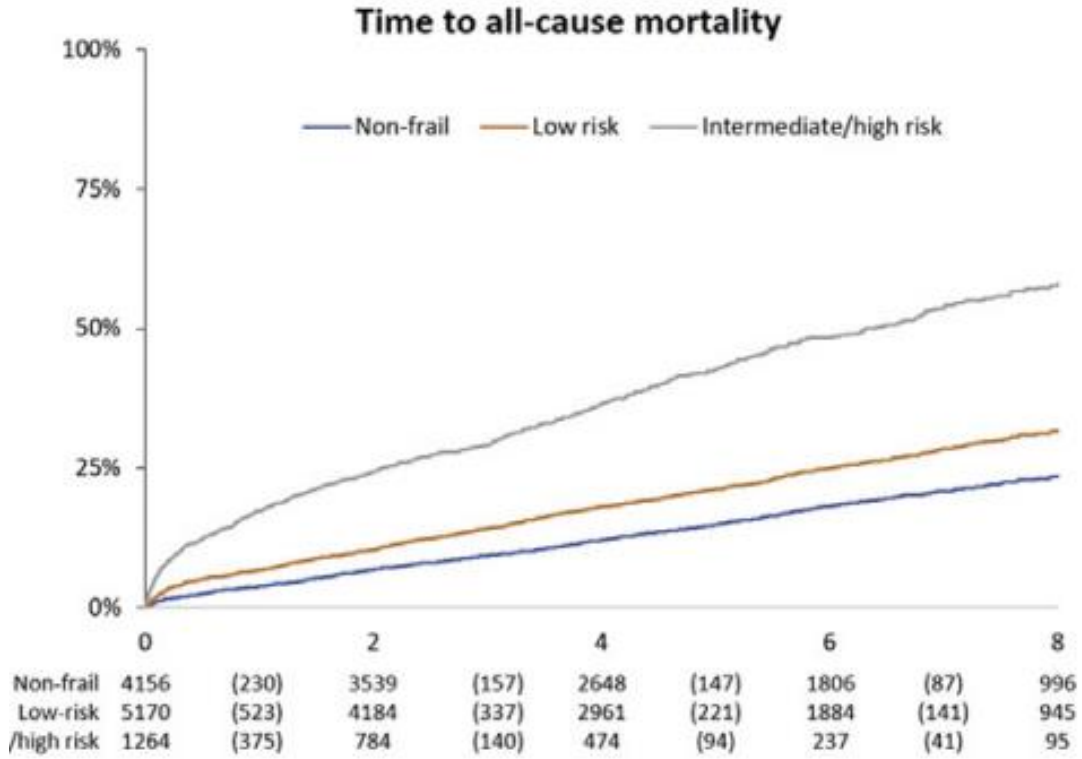
The University of Manitoba IBD Epidemiology Database includes all Manitobans with IBD from 1 April 1984 through 31 March 2018 and matched controls

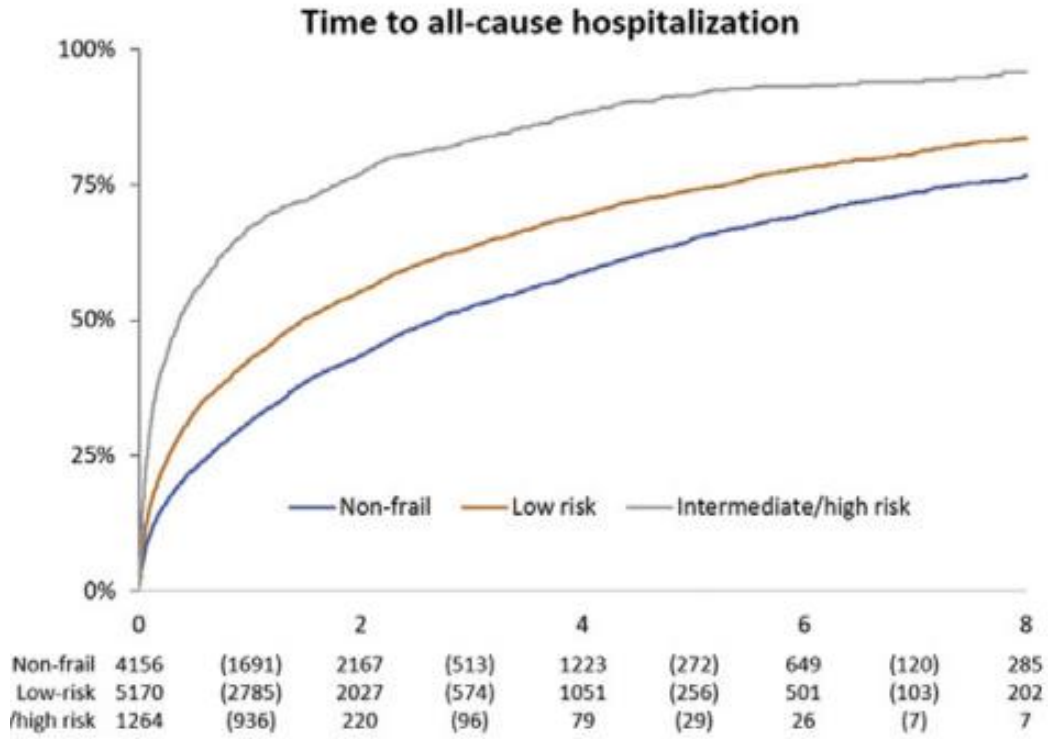
Bernstein CN, et al. Aliment Pharmacol Ther. 2021

Prevalence and Implications of Frailty in Older Adults With Incident IBD: A Nationwide Cohort Study

Hospital Frailty Risk Score
Protein calorie malnutrition
Delirium
Urinary Incontinence
Senility
Reduction in walking

- ICD-10 Codes based-study
- Nationwide, population-based Swedish cohort
- Incident IBD cases 2007-2016
- Adults ≥60 years with incident IBD have higher prevalence of frailty vs matched non-IBD population (61% vs 27%)

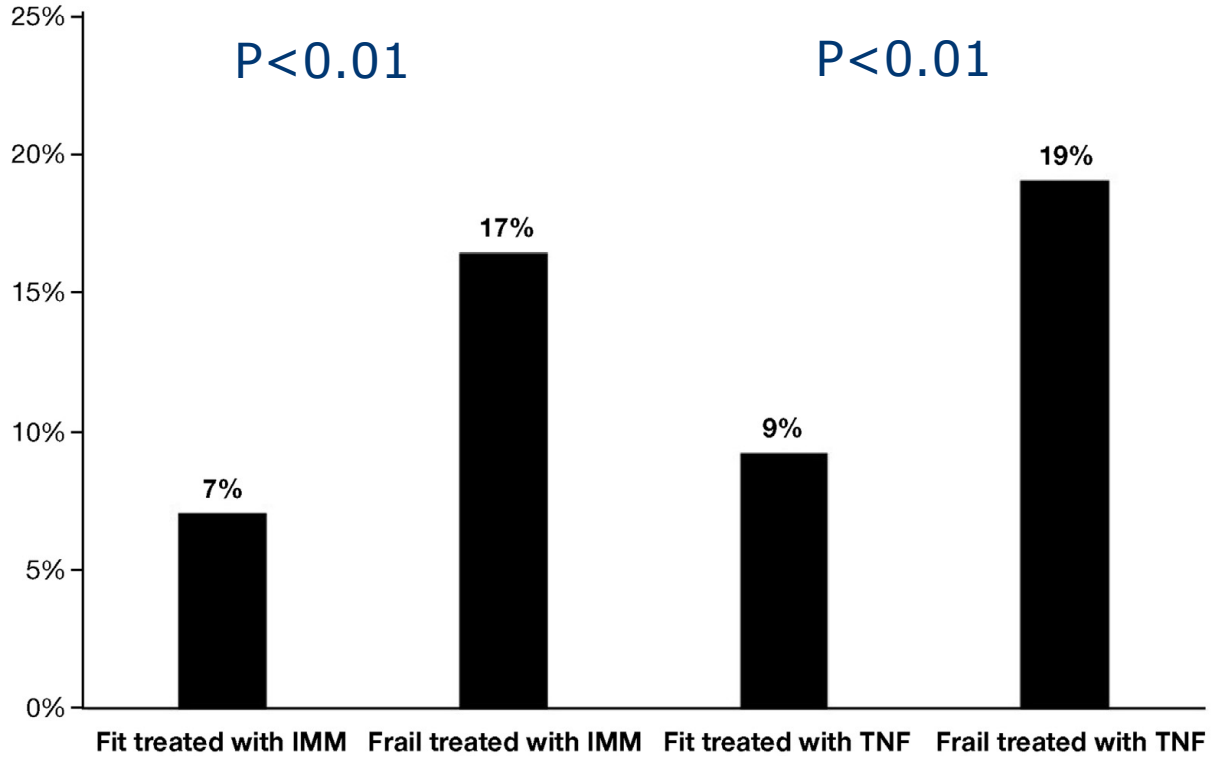




Kochar B, et al. CGH 2022

Pretreatment Frailty Is Independently Associated With Increased Risk of Infections After Immunosuppression in Patients With IBD

cohort study of 11,001 patients with IBD



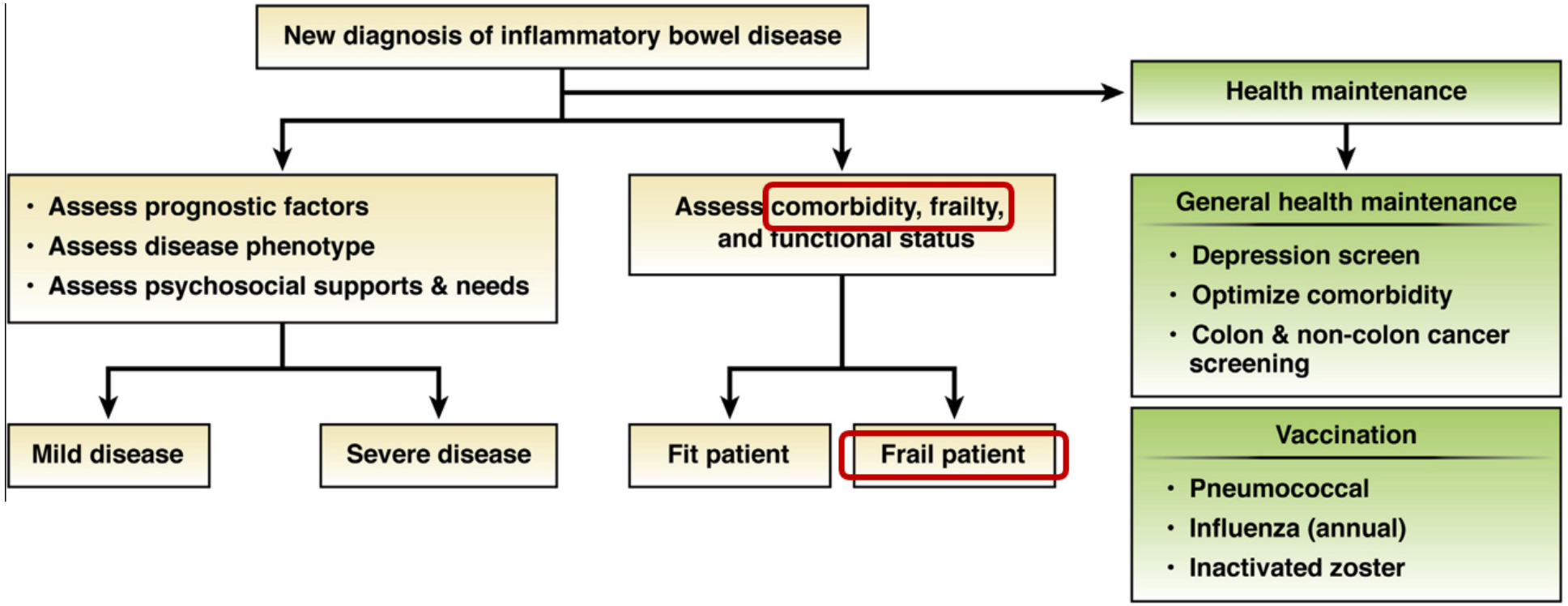
Risk of infections after immunosuppression in patients with IBD, stratified by presence and absence of frailty-related diagnoses in the 2 years before treatment

Supplementary Table 1.ICD-9 Codes Used to Identify Frailty

ICD-9 Code	Diagnosis description
263.8	Other protein calorie malnutrition
263.9	Unspecified protein calorie malnutrition
293.1	Subacute delirium
294	Persistent mental disorders due to conditions classified elsewhere
719.7	Difficulty in walking
788.3	Urinary incontinence
797	Senility without psychosis
799.89 v46.3	Other ill-defined conditions Wheelchair dependence
v69.9	Unspecified problem related to lifestyle

Kochar B, et al. Gastroenterology 2020

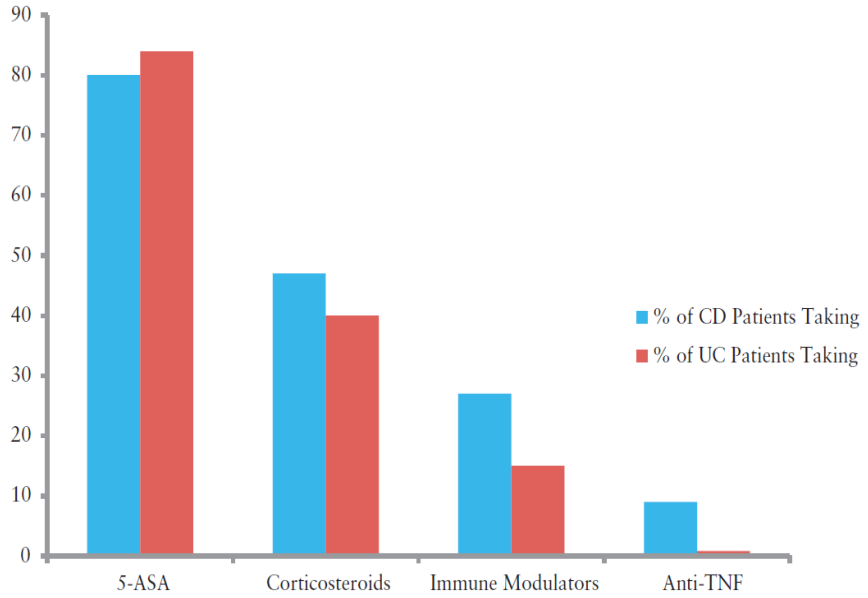
Management algorithm for elderly patients with IBD

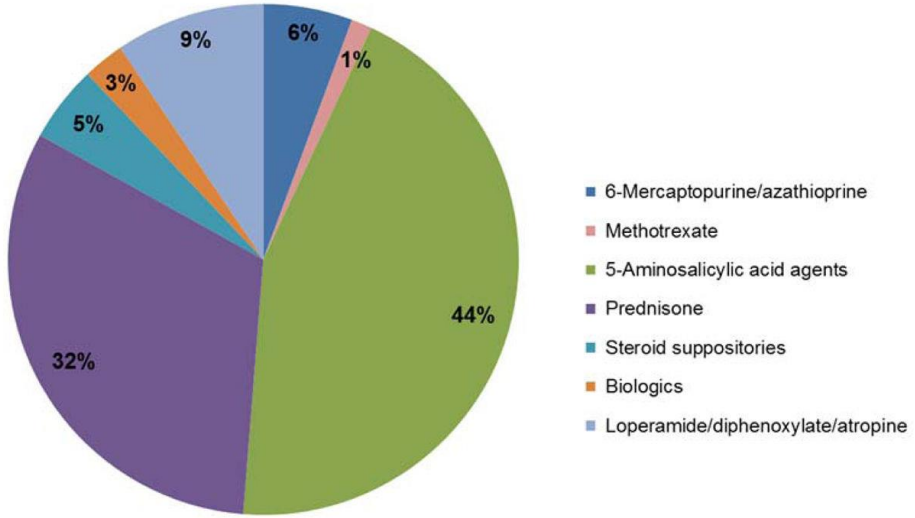


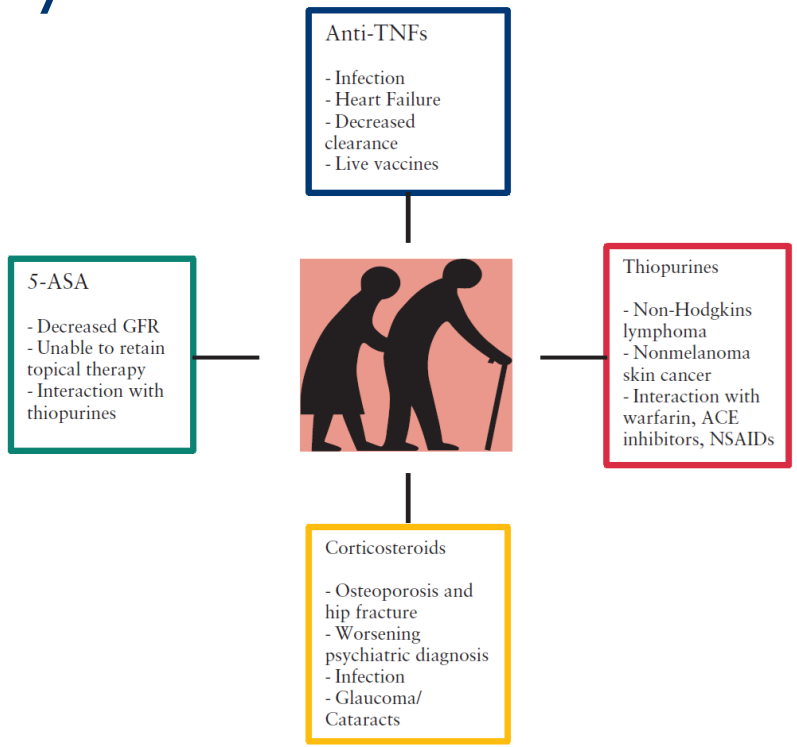
1) Multidisciplinary approach
2) Similar principles behind selection of optimal therapy
3) Safety considerations
4) Overall fitness and frailty assessment

Adapted from Ananthakrishnan AN, et al. Gastroenterology 2021

IBD medication consideration in the elderly







Maintenance steroid use in elderly IBD

IBD age group (years)	Average dose of prednisone (mg/day)	Percent steroid use
65–70	17.2	43.1
71–75	17.6	23.9
76–80	21.7	19.3
81–85	17.0	12.5
86 and above	10.0	1.1

Taleban S, et al. JCC 2015; Ananthakrishnan AN, et al. IBD 2017; Juneja M, et al. Dig Dis Sci 2012

Systematic Review of Inclusion and Analysis of Older Adults in Randomized Controlled Trials of Medications Used to Treat IBD

TABLE 1. Trials Included in a Systematic Review of RCTs of Medications Approved for the Treatment of IBD

	n
Total number of manuscripts	46
Trials of nonimmunosuppressive medications (%)	4 (9)
Trials of biologics (%)	29 (63)
Trials of other immunosuppression medications (%)	13 (28)
Range of mean age	31-45 y
Range of median age	25-45 y
RCTs that indicated whether adults aged ≥65 y were included (%)	26 (57)
RCTs that reported an age-specific subgroup analysis (%)	5 (11)
RCTs that reported an upper age limit as an exclusion (%)	18 (39)
Upper age limit: 65 y	1 (2)
Upper age limit: 70 y	4 (9)
Upper age limit: 75 y	8 (17)
Upper age limit: 80 y	4 (9)
Upper age limit: 85 y	1 (2)
Exclusion criteria that disproportionately affect older adults (%)	
History of malignancy	25 (59)
Nonmalignant, noninfectious comorbidities	29 (64)
Functional status	0
Cognitive impairment	1 (2)
RCTs with functional status as an outcome	0

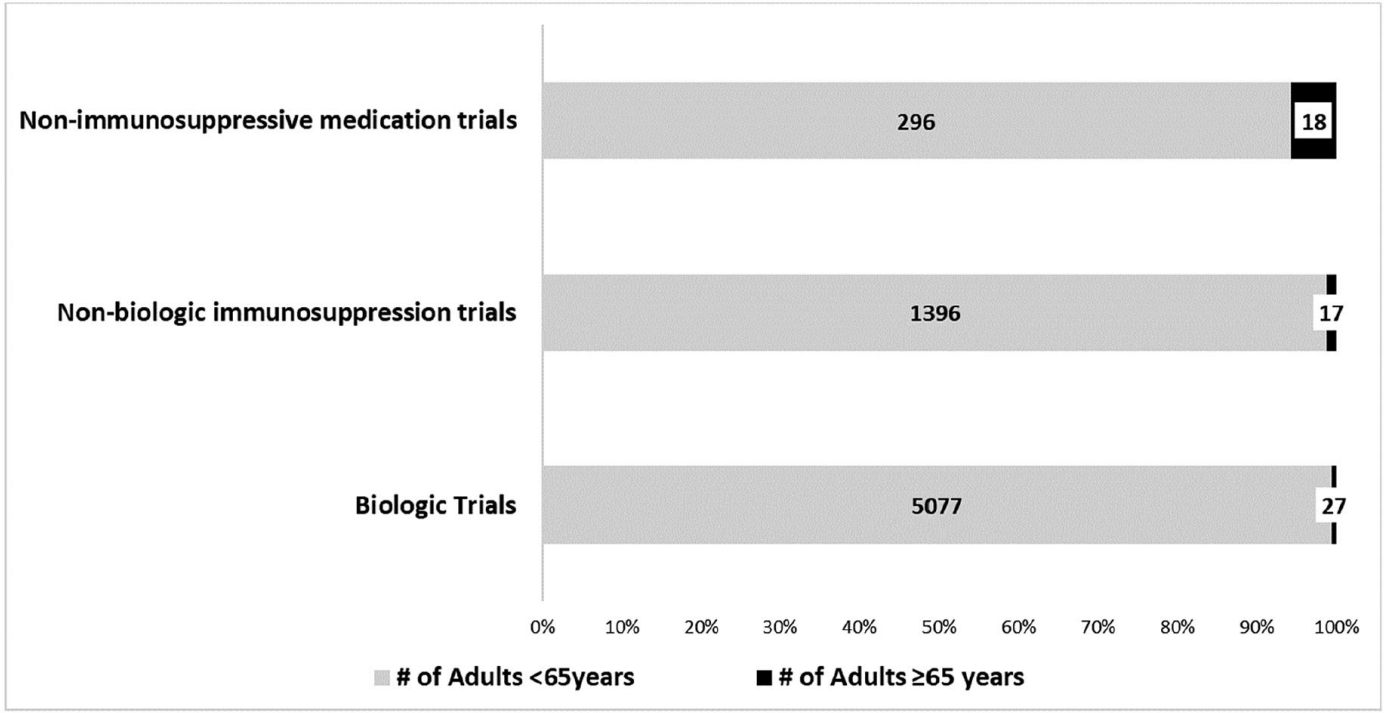
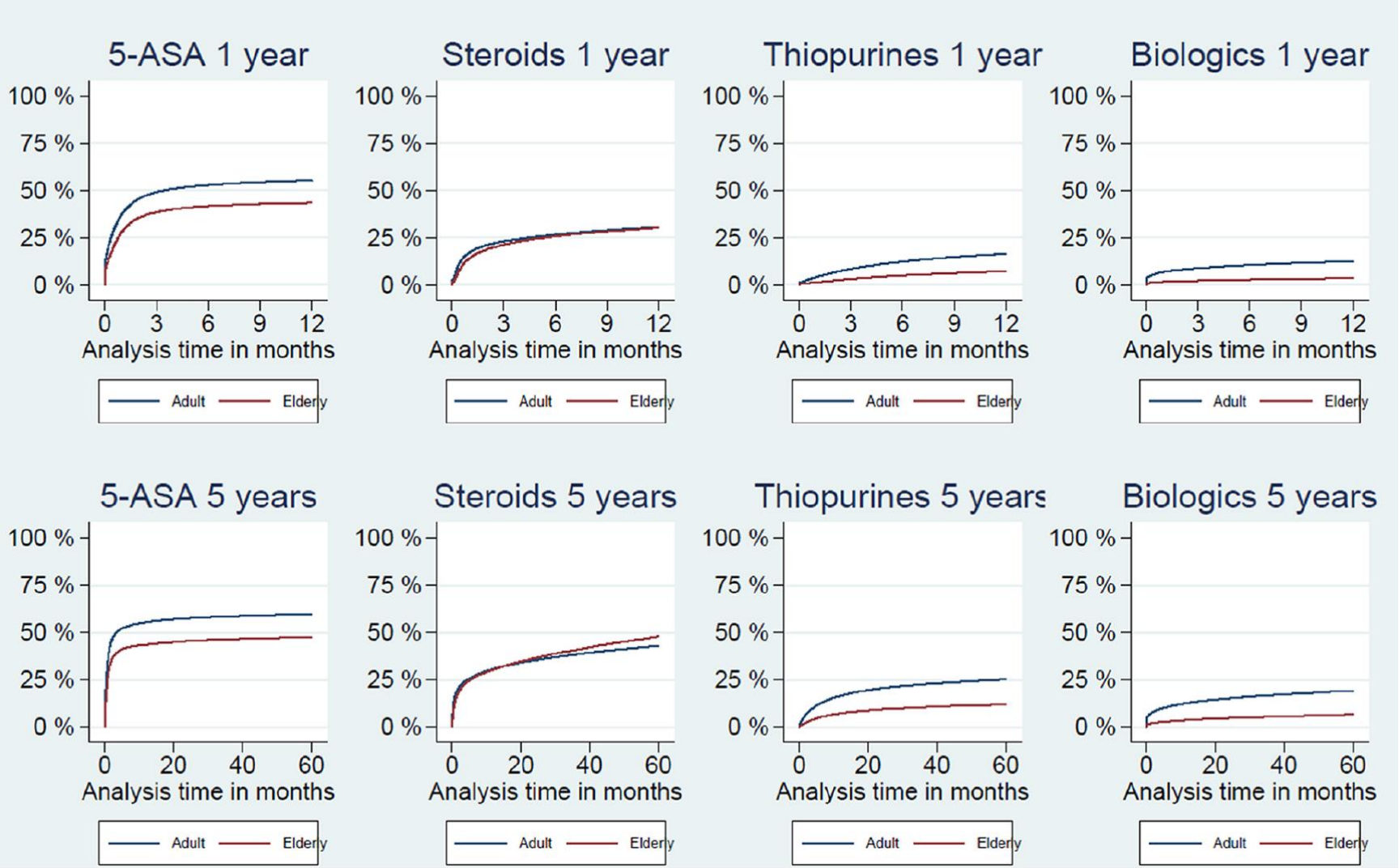


FIGURE 1. Older adult inclusion in RCTs of medications approved to treat IBD stratified by class of medication.

Kochar B, et al. IBD 2021

Patients with elderly onset IBD have a decreased chance of initiation of all types of medications



1995 to 2020: elderly (*N* = 19,187) and adult onset (*N* = 49,852)

Norgard BM, et al. Aliment Pharmacol Ther 2023

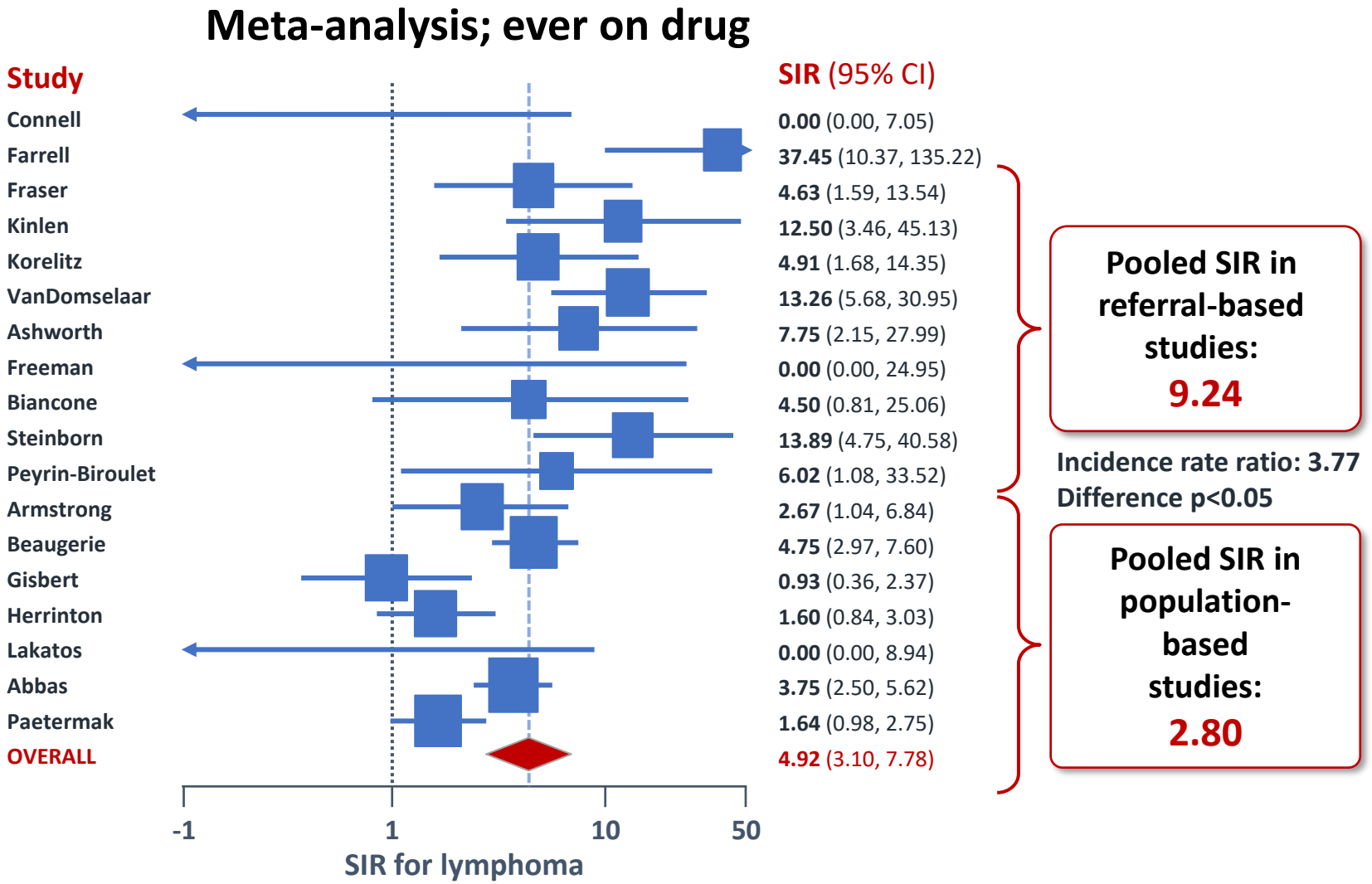
Corticosteroids use and risk of serious infections

IBD patients	Cases	Controls	Crude RR	Adjusted[a] RR
Corticosteroid exposure	***N* (%)**	***N* (%)**		**(95% CI)**
All IBD patients				
No use	352 (62.4)	2,156 (81.5)	1.0 (Reference)	1.0 (Reference)
Ever use	212 (37.6)	490 (18.5)	3.2	2.3 (1.8–2.9)
Current use	149 (26.4)	287 (10.8)	3.8	2.8 (2.1–3.7)
Past use	63 (11.2)	203 (7.7)	2.2	1.6 (1.1–2.2)
46–90 Days	31 (5.5)	95 (3.6)	2.4	1.7 (1.0–2.7)
91–135 Days	20 (3.6)	56 (2.1)	2.6	1.5 (0.8–2.8)
136–180 Days	12 (2.1)	52 (2.0)	1.6	1.4 (0.7–2.8)

RR, relative risk; CI, confidence interval

Brassard P, et al. Am J Gastroenterol 2014

IBD, lymphomas and thiopurines



- Increased risk in current users (5.71; 95% CI 3.72, 10.1)
- Level of risk significant after 1 year of exposure (4.31; 95% CI 1.85, 10.1)
- Highest relative risk in patients younger than 30 years (6.99; 95% CI 2.99, 16.4)
- **Highest absolute risk in patients older than 50 years (1:377 cases per patient-year)**

CI, confidence interval; SIR, standardised incidence ratio. Weights are from random effects analysis

Kotlyar DS, et al. Clin Gastroenterol Hepatol 2015

Thiopurines and age-dependent risk of non-melanoma skin cancer

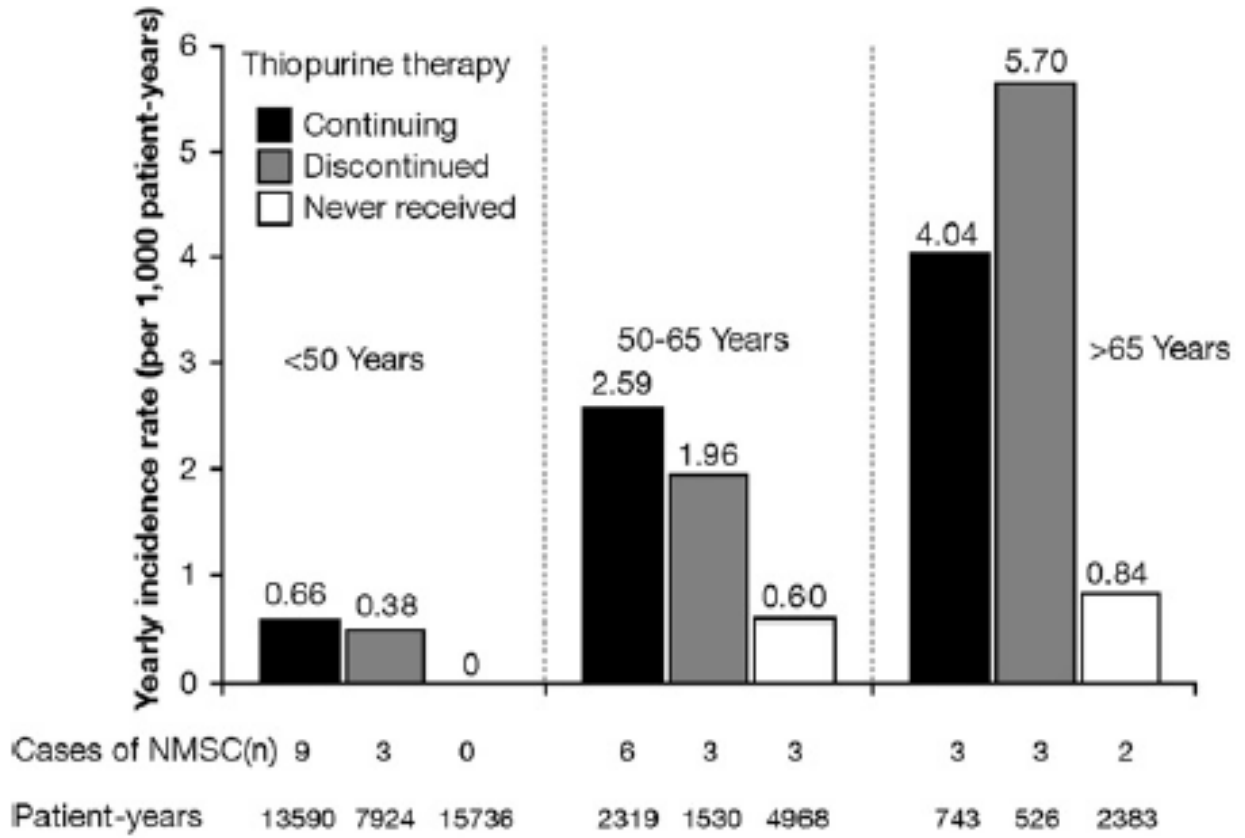
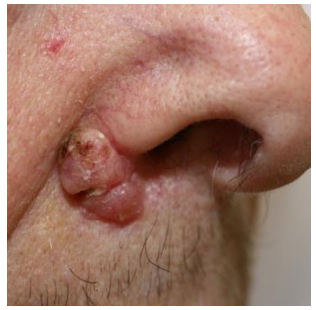


FIgure 1. Incidence rates of NMSC according to thiopurine exposure grouped by age at entry in the cohort.



Peyrin-Biroulet L, et al. Gastroenterology 2011

Advanced Age is Risk Factor for Severe Infections and Mortality in Patients Given anti-TNF alpha for IBD

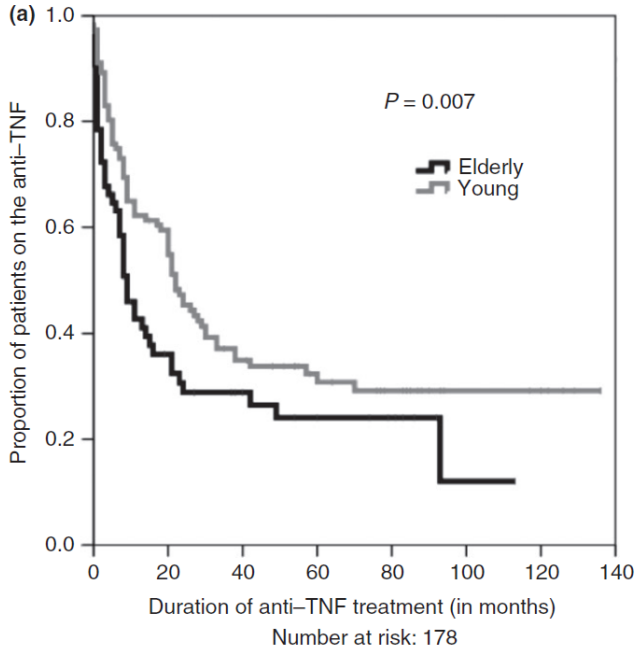
	95 elderly patients treated with biologics		190 adult matched controls treated with biologics		190 elderly controls not treated with biologics	
	UC	CD	UC	CD	UC	CD
Pts n°	37	58	74	116	74	116
Male/female	20/17	35/23	40/34	70/46	40/34	70/46
Mean age(range)	71 (65-81)	71(65-84)	38(17-64)	39(16-64)	71(65-81)	70(65-80)
Remission n° (%)	22 (59.5)	38 (65.5)	42(56.7)	68 (58.6)	-	-
Maintenance n° (%)	12 (32.4)	39 (67.2)	24 (32.4)	78 (67.2)	-	-
Comorbidity n° (%)	35(94.5%)	44 (75.8)	4 (5.4)	6 (5.1)	37 (50)	46(39.6)
Deaths (n°)	**4**	**6**	0	2	2	3
Severe infections (n°)	**5**	**6**	2	3	1	0
Cancer (n°)	1	1	0	0	1	3
Steroids (n°)	36	54	72	108	74	104
Association anti-TNF+AZA/6MP/MTX n(%)	7 (19)	15 (26)	17 (23)	32 (28)	-	-

AZA, azathioprine; MP, mercaptopurine; MTX, methotrexate

Cottone M, et al. Clin Gastroenterol Hepatol. 2011

Anti-TNFs in elderly IBD patients

Retrospective, single-center study: 66 IBD patients (CD 32) initiating anti-TNF over the age of 65 years (median age 70, IQR 66.5-73)



Relative risk for adverse events (AE) and severe adverse events (SAE)

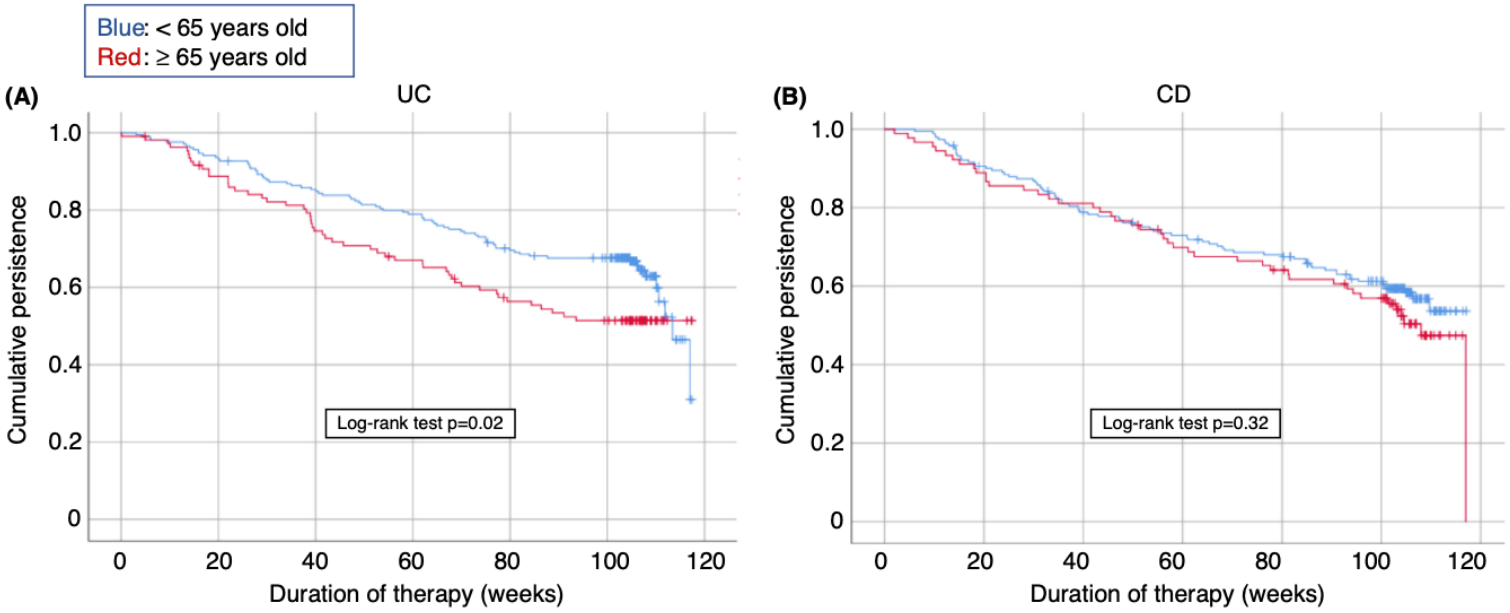
	Event rate per year in cases: ≥65 anti-TNF (n = 66)	Event rate per year in controls <65 anti-TNF (n = 112)	Relative risk for cases: ≥65 anti-TNF RR (95% CI)	P*
AE without hospitalisation				
(a) Only under anti-TNF	0.08	0.08	0.95 (0.39–2.33)	0.911
(b) Under anti-TNF and IMS	0.28	0.14	2.11 (0.68–6.58)	0.212
(c) Under anti-TNF and CS	0.72	0.25	4.52 (2.18–9.37)	<0.001
SAE				
(a) Only under anti-TNF	0.50	0.14	4.87 (2.42–9.82)	<0.001
(b) Under anti-TNF and IMS	0.50	0.26	2.73 (0.67–11.12)	0.160
(c) Under anti-TNF and CS	1.64	0.34	4.85 (1.89–6.12.46)	0.020

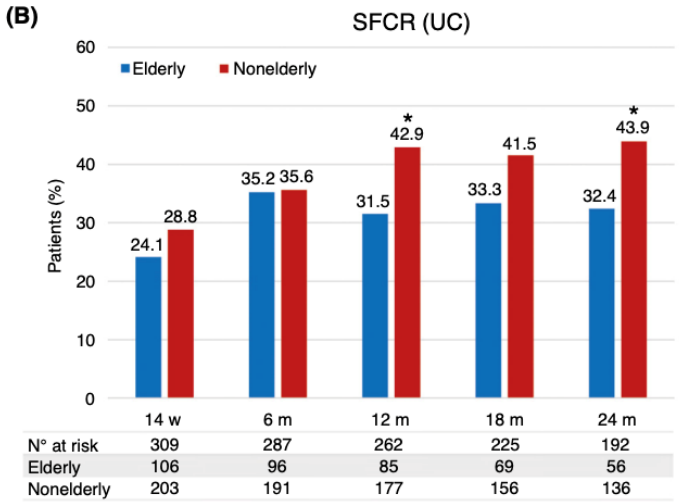
IMS, immunosuppressants; CS, corticosteroids; CI, confidence interval

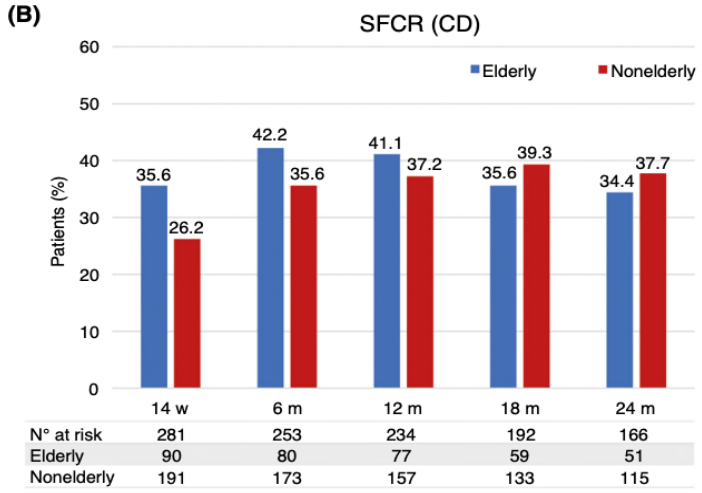
Age older than 65 and CCI>0 were independent risk factors for malignancy and mortality regardless of the medication

Lobaton T, et al. APT 2015

Effectiveness and safety of vedolizumab in a matched cohort of elderly and nonelderly patients with IBD: the IG-IBD LIVE study



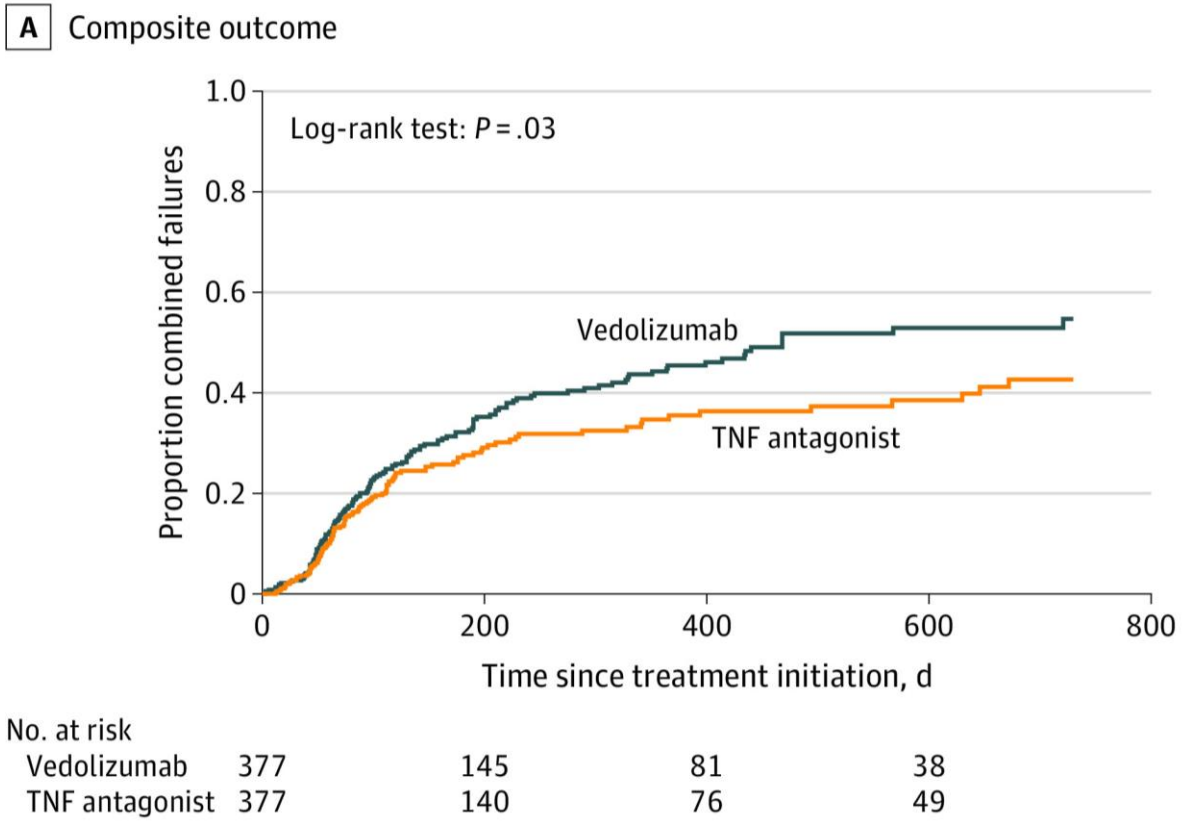




On multivariate analysis, a CCI ≤2 was protective from developing any adverse event (OR = 0.44, 95% CI, 0.26– 0.77, p= 0.004)

Pugliese D, et al. APT 2022

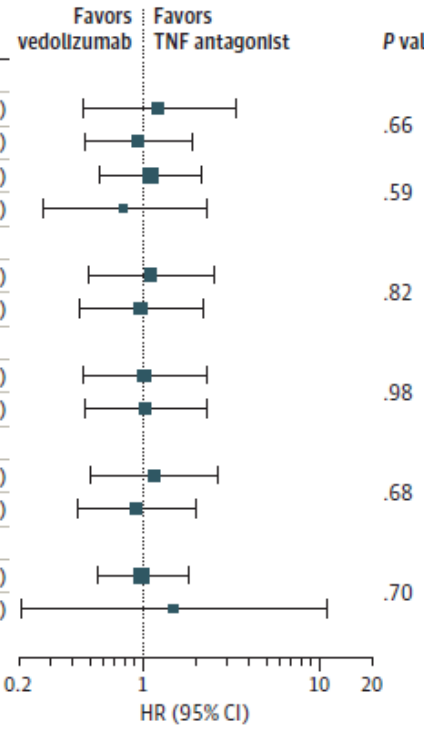
Comparative Outcomes and Safety of Vedolizumab vs anti-TNFs for Older Adults With IBD



Difference in term of effectiveness outcome
HR (95%, CI) 1.31 (1.02-1.69)

Figure 3. Subgroup Analysis Comparing Risk of Serious Infections Among Older Patients With Inflammatory Bowel Disease (IBD) Treated With Vedolizumab vs Tumor Necrosis Factor (TNF) Antagonists

Subgroup	Events, No./patients, No. (%) Vedolizumab	TNF antagonist	HR (95% CI)	P value
Age, y				
50-60	9/196 (4.6)	7/193 (3.6)	1.24 (0.46-3.39)	.66
≥60	17/181 (9.4)	17/184 (9.2)	0.95 (0.47-1.91)	
50-70	19/305 (6.2)	17/309 (5.5)	1.11 (0.57-2.18)	.59
≥70	7/72 (9.7)	7/68 (10.3)	0.79 (0.27-2.30)	
CCI score				
0	13/249 (5.2)	11/257 (4.3)	1.12 (0.50-2.53)	.82
≥1	13/128 (10.2)	13/120 (10.8)	0.98 (0.44-2.19)	
Sex				
Female	13/202 (6.4)	12/206 (5.8)	1.03 (0.46-2.30)	.98
Male	13/175 (7.4)	12/171 (7.0)	1.05 (0.47-2.34)	
IBD subtype				
Crohn disease	12/177 (6.8)	11/182 (6.0)	1.17 (0.51-2.70)	.68
Ulcerative colitis	14/200 (7.0)	13/195 (6.7)	0.93 (0.43-1.99)	
Treatment				
Monotherapy	≥5/352 (NA)	≥5/335 (NA)	1.00 (0.55-1.81)	.70
Concomitant thiopurine	<5/25 (NA)	<5/42 (NA)	1.50 (0.21-11.0)	



No difference in term of primary safety outcome HR (95%, CI) 1.17 (0.51-2.70)

Singh S, et al. JAMA OPEN 2022

Effectiveness and Safety of Ustekinumab in Elderly Patients with Crohn's Disease: Real World Evidence From the ENEIDA Registry

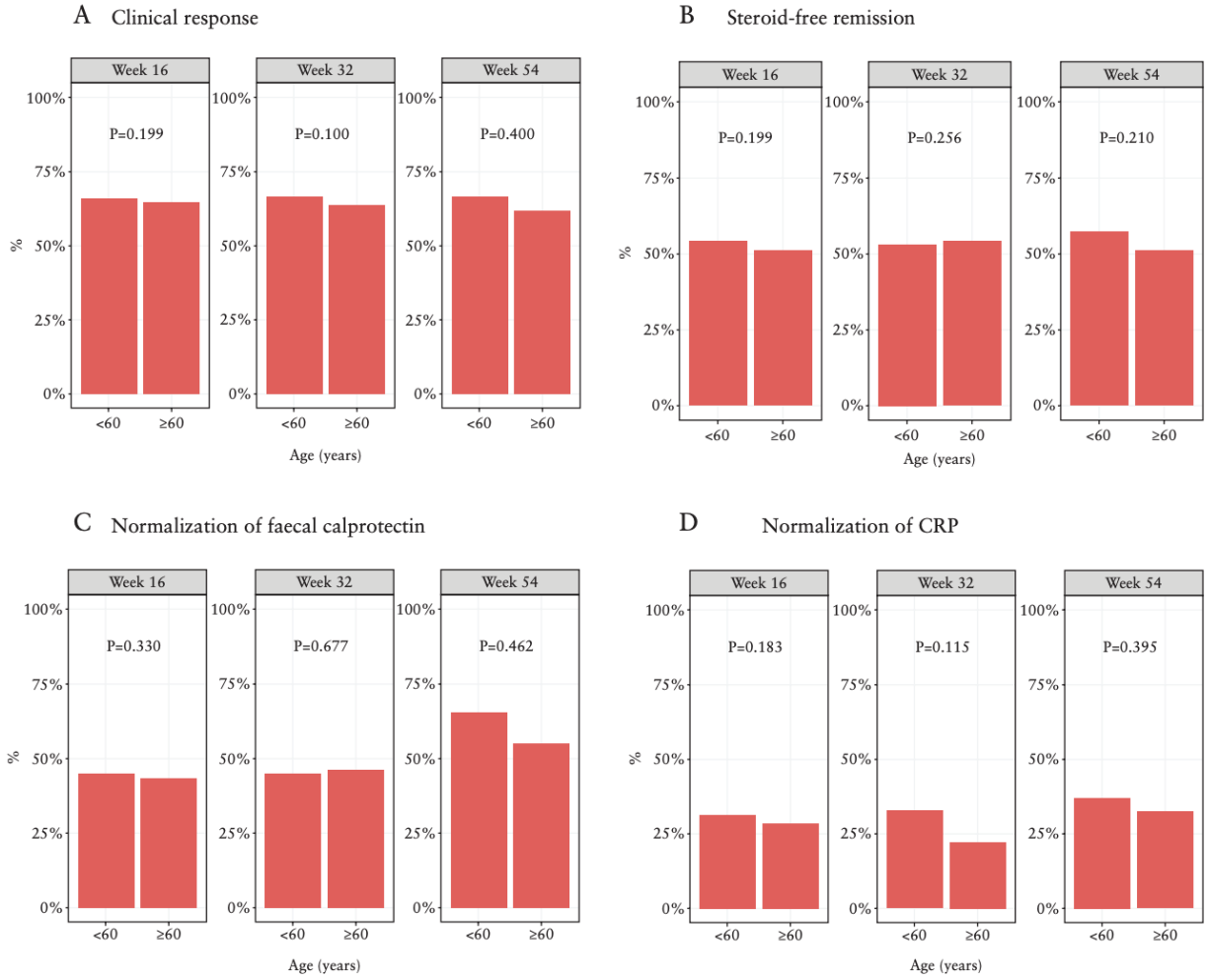


Table 4. Safety variables throughout the follow-up period

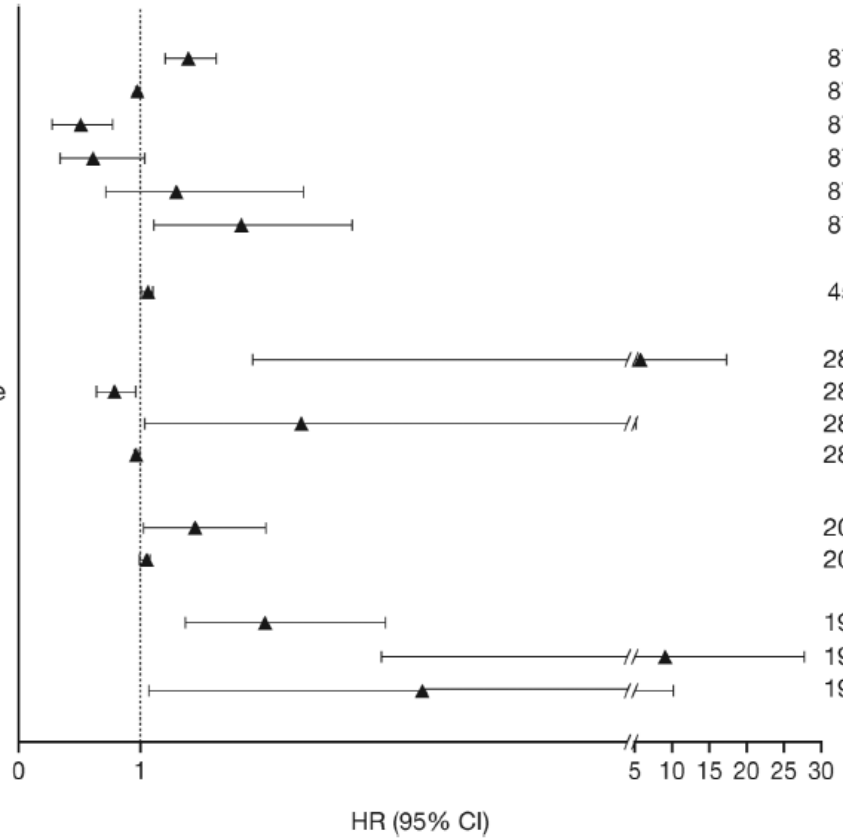
Variable	Non-elderly patients	Elderly patients	*p* value
Adverse events	49 [11.2%]	30 [14.2%]	0.35
Worsening extraintestinal manifestations	23 [5.28%]	10 [4.74%]	0.92
Worsening perianal disease	15 [3.44%]	2 [0.94%]	0.11
Severe infection	32 [7.34%]	15 [7.08%]	1.00
Development of neo-plasms	3 [0.69%]	9 [4.25%]	0.003

Non-elderly patients [N = 436] Elderly patients [N = 212]

Casas-Deza D, et al. JCC 2023

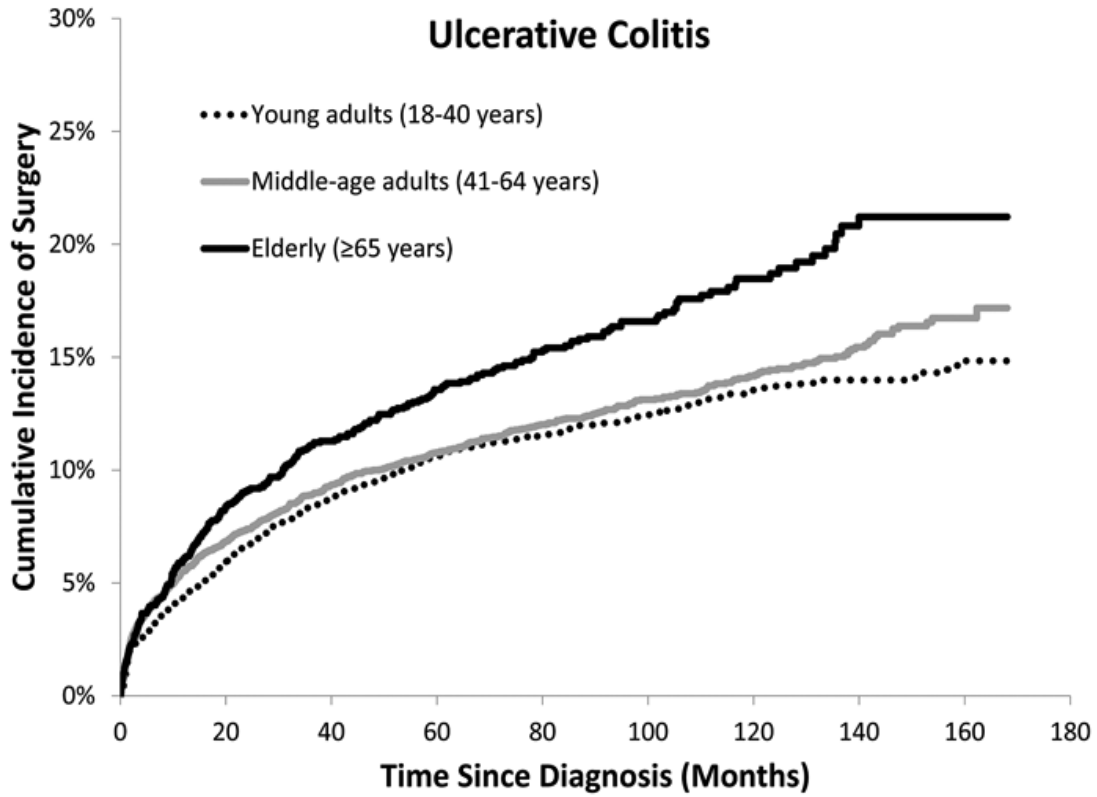
Age as a Risk Factor for HZ and Malignancy in the Overall UC Cohort

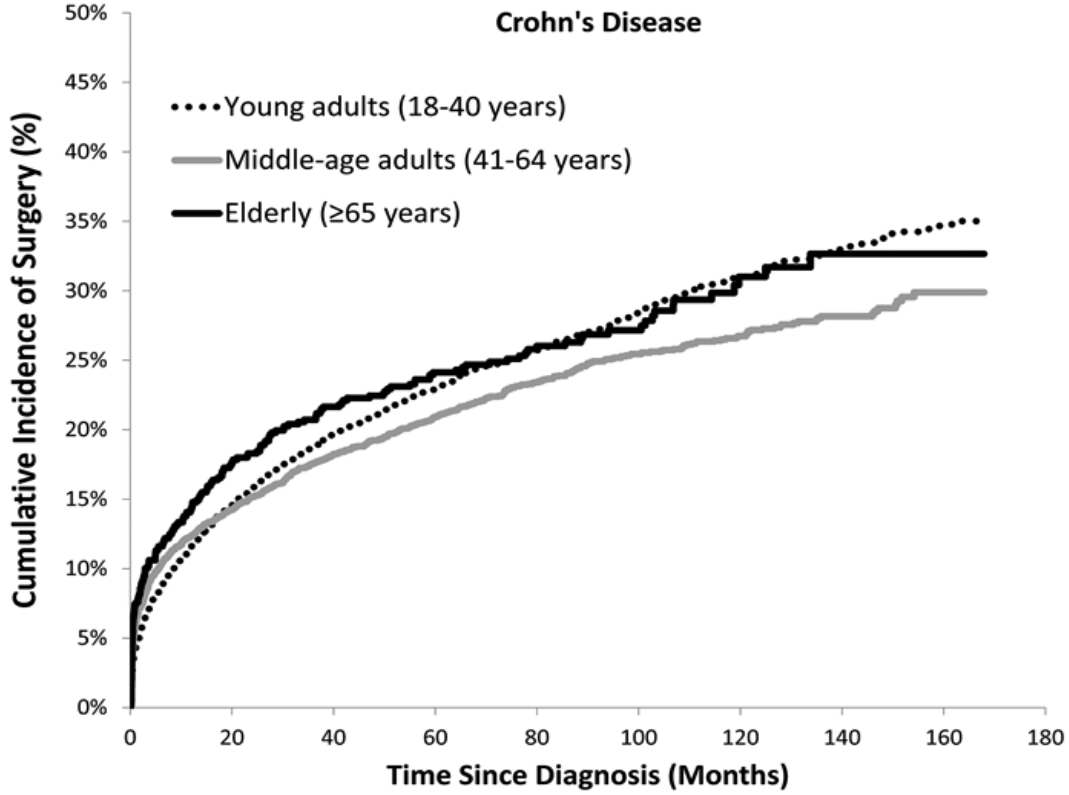
AESI	Factor	Comparison	n/N	HR (95% CI)	Factor *P*-value
Herpes zoster	Age	Per 10-year increase	87/1157	1.40 (1.21-1.63)	< 0.0001
	Weight	Per 1-kg increase	87/1157	0.98 (0.96-0.99)	0.0030
	Region	Europe vs North America	87/1157	0.47 (0.28-0.78)	0.0117
	Region	Europe vs Other	87/1157	0.61 (0.35-1.04)	0.0117
	Region	North America vs Other	87/1157	1.30 (0.72-2.34)	0.0117
	Prior TNFi failure	Yes vs No	87/1157	1.76 (1.13-2.74)	0.0128
Serious infections	Body mass index	Per 1-kg/m² increase	45/1157	1.06 (1.01-1.11)	0.0114
Opportunistic infections	Diabetes mellitus	Yes vs No	28/1124†	5.78 (1.92-17.36)	0.0018
	Baseline absolute neutrophil count	Per 1×10^9 cells/L increase	28/1124†	0.79 (0.65-0.97)	0.0214
	Prior TNFi failure	Yes vs No	28/1124†	2.32 (1.04-5.18)	0.0391
	Weight	Per 1-kg increase	28/1124†	0.97 (0.95-1.00)	0.0467
Malignancy (excluding NMSC)	Age	Per 10-year increase	20/1124†	1.45 (1.03-2.04)	0.0330
	Prior duration of UC	Unit = 1 year	20/1124†	1.05 (1.00-1.09)	0.0372
NMSC	Age	Per 10-year increase	19/1124†	2.03 (1.37-3.02)	0.0004
	Prior NMSC	Yes vs No	19/1124†	9.09 (2.98-27.73)	0.0001
	Prior TNFi failure	Yes vs No	19/1124†	3.32 (1.08-10.20)	0.0363



Lichtenstein GR et al. Inflamm Bowel Dis 2023

Cumulative risk of surgery related to IBD among patients with UC and CD stratified by age at diagnosis





Incident IBD cases between 1999 and 2008

Nguyen GC, et al. IBD 2016

Increased Postoperative Mortality and Complications Among Elderly Patients With IBD

Table 2. Short-Term Outcomes After Abdominal Surgery for Inflammatory Bowel Disease

Outcomes	All IBD (N = 15,495)	Crohn's disease		Ulcerative colitis	
		Elderly (n = 736)	Nonelderly (n = 7524)	Elderly (n = 971)	Nonelderly (n = 6264)
30-day mortality, %	1.0%	4.2%	0.3%[a]	6.1%	0.7%[a]
Infectious complications, %	15.4%	16.2%	13.6%	24.7%	16.0%[a]
Deep wound, %	1.9%	1.2%	2.0%	1.7%	2.0%
Intra-abdominal, %	6.9%	7.1%	6.4%	7.7%	7.2%
Sepsis, %	6.4%	4.6%	5.9%	7.6%	6.9%
Septic shock, %	1.6%	3.5%	1.2%[a]	4.5%	1.3%[a]
Pneumonia, %	2.0%	4.4%	1.6%[a]	6.3%	1.5%[a]
Urinary tract infection, %	3.5%	3.9%	2.6%[b]	7.0%	4.1%[a]
Wound dehiscence, %	1.5%	1.8%	1.3%	2.8%	1.4%[c]
Bleeding requiring transfusion, %	6.8%	12.1%	5.6%[a]	14.3%	6.6%[a]
Cardiac complications, %	0.5%	2.3%	0.2%[a]	2.6%	0.3%[a]
Myocardial infarction, %	0.3%	1.2%	0.1%[a]	1.4%	0.1%[a]
Cardiac arrest, %	0.3%	1.2%	0.1%[a]	1.2%	0.2%[a]
Neurologic complications, %	0.3%	0.5%	0.1%[b]	1.0%	0.2%[a]
Cerebrovascular accident, %	0.1%	0.4%	0.01%[c]	0.3%	0.1%
Coma, %	0.1%	0.1%	0.01%	0.6%	0.1%[a]
Peripheral nerve injury, %	0.1%	0.0%	0.1%	0.1%	0.1%
Renal complications, %	1.1%	2.2%	0.6%[a]	3.1%[d]	1.2%[a]
Acute renal failure, %	0.4%	1.1%	0.2%[c]	1.5%[d]	0.4%[a]
Progressive renal insufficiency, %	0.7%	1.1%	0.5%[b]	1.9%[d]	0.8%[a]
Venous thromboembolism, %	2.5%	3.1%	1.5%[c]	4.3%	3.3%
Deep venous thrombosis, %	2.0%	2.9%	1.2%[a]	3.6%	2.7%
Pulmonary embolism, %	0.7%	0.8%	0.5%	1.1%	0.8%
Hospital stay > 30 days, %[d]	2.2%	5.9%	1.5%[c]	4.1%	2.2%
Readmission within 30 days, %[d]	18.5%	13.7%	16.3%	24.2%	20.9%
Proportion unplanned, %	98.2%	94.4%	99.1%	100%	97.3%
Re-operation within 30 days, %[d]	7.1%	9.0%	6.4%	7.4%	7.6%
In-hospital death, %[d]	0.7%	3.4%	0.3%[a]	3.2%	0.6%[a]

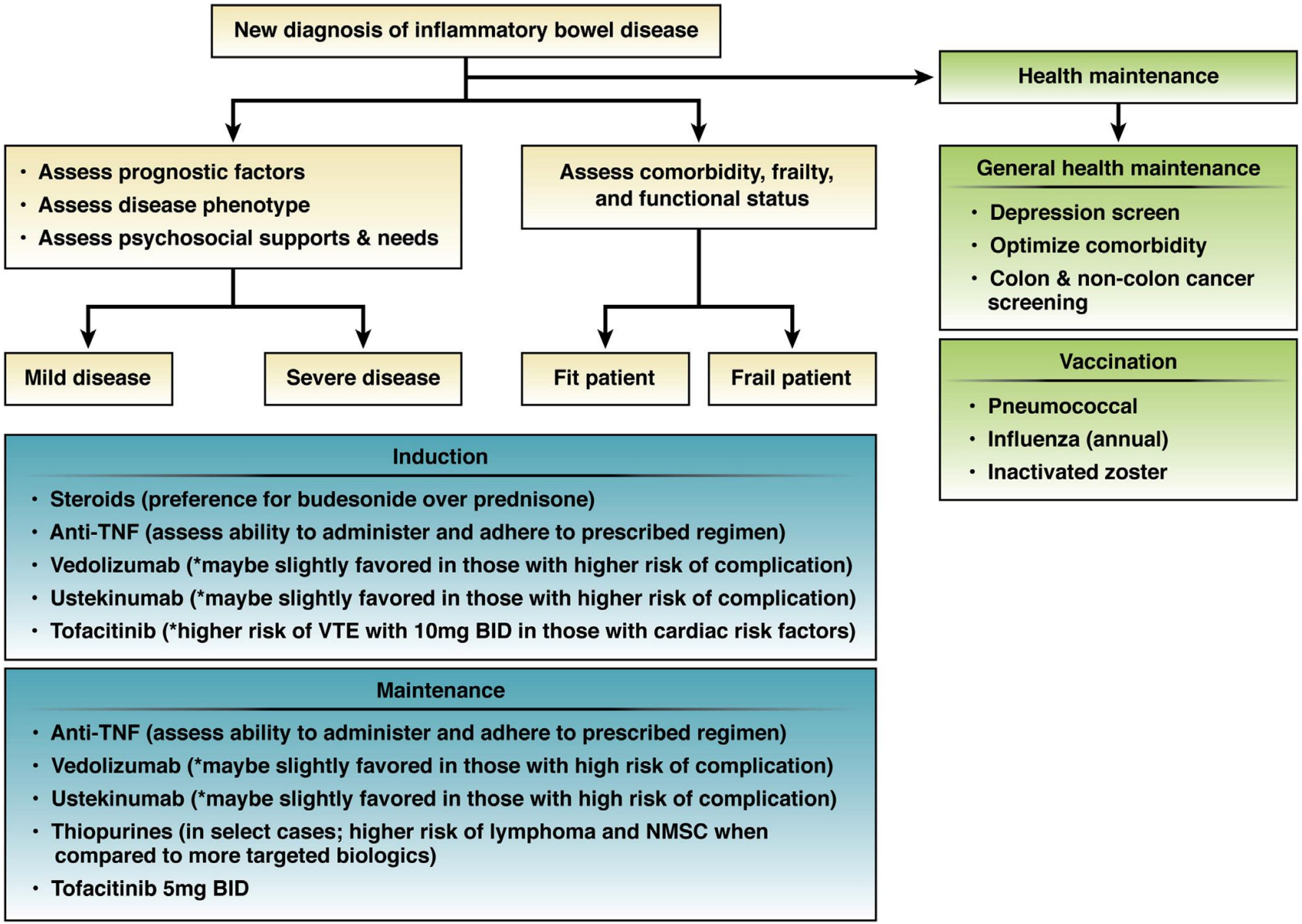
[a] $P < .001$.
[b] $P < .05$.
[c] $P < .01$.
[d] 2011 to 2012 subgroup.

Table 3. Types of Abdominal Surgery Among Elderly and Nonelderly IBD Patients and Postoperative Outcomes

Surgical procedure	Frequency N (%)		Rate of postoperative complications (%)		Cumulative 30-day mortality (%)	
	Elderly	Nonelderly	Elderly	Nonelderly	Elderly	Nonelderly
Small-bowel resection						
Laparoscopic	18 (1%)	245 (2%)[a]	0%	13%	0%	0%
Open	100 (6%)	805 (6%)	26%	18%	5.0%	0.5%[b]
Total colectomy						
Laparoscopic	165 (10%)	2029 (15%)[b]	22%	13%[b]	3.0%	0.1%[b]
Open	502 (29%)	2417 (18%)[b]	45%	32%[c]	8.6%	1.4%[b]
Partial colectomy						
Laparoscopic	244 (14%)	2139 (16%)	35%	23%[c]	2.9%	0.2%[b]
Open	417 (24%)	3015 (22%)[a]	35%	22%[c]	6.0%	0.6%[b]
Proctectomy						
Laparoscopic	19 (1%)	251 (2%)[a]	26%	21%	0%	0%
Open	111 (7%)	1398 (10%)[b]	31%	23%	0.9%	0%
Stricturoplasty	≤10	68 (0.5%)	100%	12%	0%	0%
Stoma formation	43 (3%)	291 (2%)	21%	17%	4.7%	1.4%
Surgery for fistula	74 (4%)	1053 (8%)[b]	22%	10%[b]	1.4%	0.1%

NOTE. Cell counts ≤10 cannot be disclosed.
[a] $P < .05$.
[b] $P \leq .001$.
[c] $P < .01$.

Treatment algorithm for elderly patients with IBD



Ananthakrishnan AN, et al. Gastroenterology 2021

Conclusions

- Comprehensive and multidisciplinary assessment of the elderly patient: priorities, then short- and long-term treatment goals
- Risk-stratify elderly patients: based on disease prognostic factors, comorbidities, frailty, to determine appropriate therapeutic strategy (age, by itself, is not everything…)
- Optimization of comorbidities to minimize risks associated with IBD and treatment (medical or surgical)
- Evolving trends in the IBD treatment goals should always be translated to the older patient before they are adopted!
- Quality of Life as the primary goal