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ORIGINAL RESEARCH

Five-Year Real-World Hard Outcomes of Vedolizumab in Inflammatory Bowel Disease: The IG-IBD LONG-LIVE Study

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ABSTRACT

Introduction: Long-term real-world data on vedolizumab outcomes remain limited: the LONG-LIVE study evaluates 5-year effectiveness and safety in a large Italian cohort.

Methods: This is a long-term extension of the multicenter LIVE study involving patients with Crohn's disease (CD) and ulcerative colitis (UC). The primary outcome was the cumulative probability of major adverse clinical outcomes (the composite of IBD-related surgeries, non-surgical hospitalizations, and serious adverse events). Secondary outcomes included cumulative incidences of IBD-related surgery and non-surgical hospitalization, vedolizumab persistence, rates of death, cancer and adverse events of special interest (AESIs), and longitudinal response group transitions; outcomes in elderly patients

Daniela Pugliese and Alessandro Armuzzi equally contributed to this work.

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(≥ 65 years) were compared to non-elderly using inverse probability weighting (IPW).
***Results*:** Overall, 782 patients were included (50.4% CD; 49.6% UC; 76.3% anti-tumor necrosis factor (TNF)-experienced; 4324.1 patient-years of follow-up). The 5-year probability of major adverse clinical outcomes was 29.4% (no difference between CD and UC). In CD, penetrating behavior (aHR 1.77) predicted higher risk of the primary endpoint, while colonic location was protective (aHR 0.51). In UC, the primary endpoint was predicted by elderly age (aHR 1.99) and comorbidity burden (aHR 1.27). Five-year cumulative incidences were 23.4% for surgery and 14.3% for non-surgical hospitalization. Patients with CD had higher hospitalization risk than patients with UC (sHR 1.80). Mortality, neoplasm diagnosis, and AESIs occurred at rates of 3.93, 3.93, and 6.27 per 1000 patient-years. Five-year drug persistence was 38.7%. Achieving deep remission within 24 months mediated the relationship between initial clinical response and sustained deep remission at last follow-up. After IPW, elderly patients had a higher risk of major adverse clinical outcomes

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and non-surgical hospitalization; AESI and cancer rates did not differ.
Conclusion: Approximately one in three patients experienced a major adverse clinical outcome over 5 years, driven primarily by disease-related complications rather than adverse events, with a consistent safety profile across age groups.

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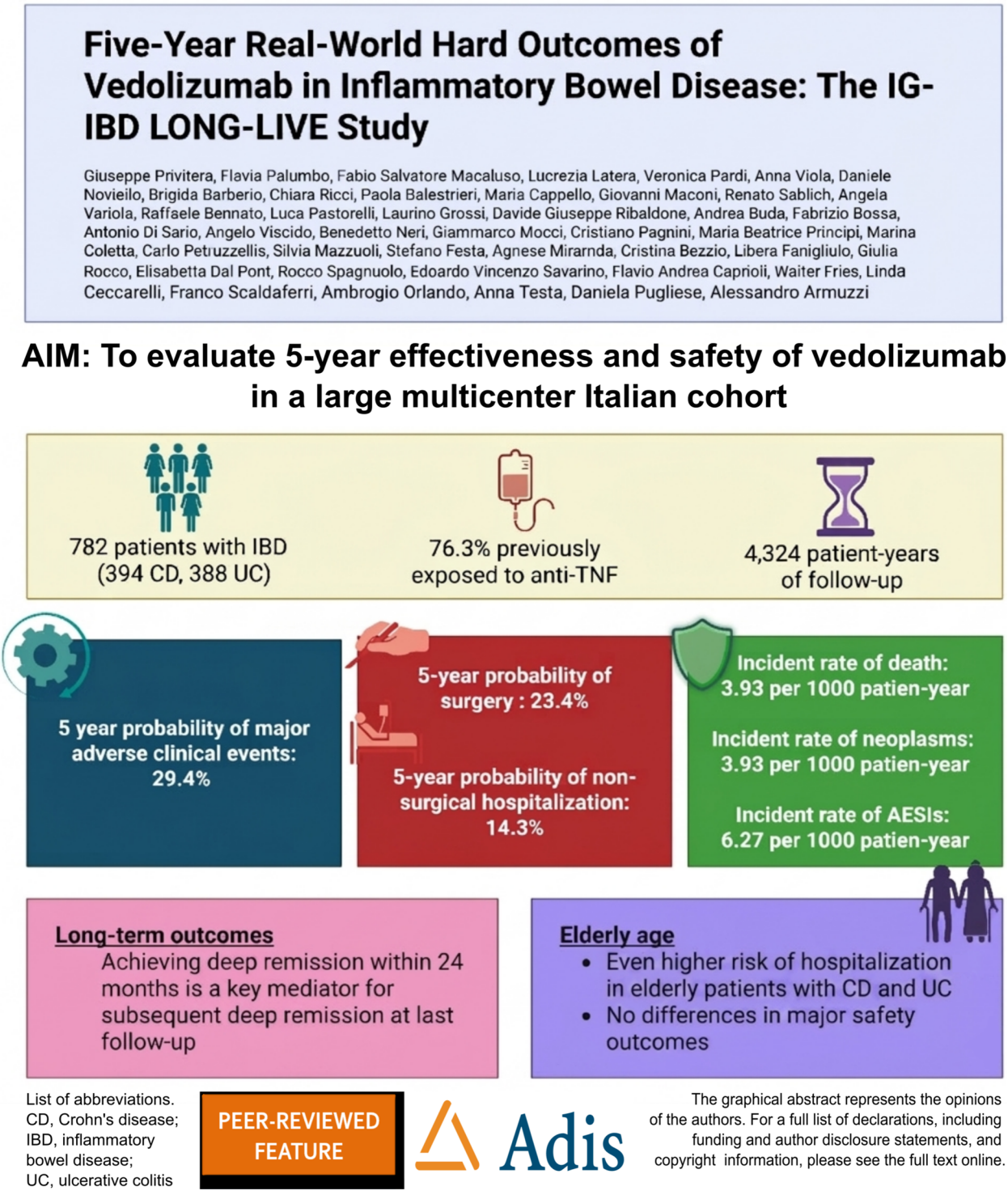
Graphical Abstract:



PLAIN LANGUAGE SUMMARY

Vedolizumab is a gut-selective biologic therapy approved for Crohn's disease (CD) and ulcerative colitis (UC). While its short-term effectiveness is well established, data on what happens to patients beyond 2 years of treatment remain limited. In this study, we followed 782 patients for up to 7 years across 47 Italian centers to track hard clinical outcomes: surgery, hospitalization, serious adverse events, and death. About one in three patients experienced a major adverse clinical outcome over 5 years—a composite endpoint that includes IBD-related surgeries, non-surgical hospitalizations, and serious adverse events—with no meaningful difference between CD and UC. Surgery occurred in approximately one in five patients, and non-surgical hospitalizations were more frequent in CD. Serious adverse events, including deaths, cancers, and infections, remained uncommon throughout follow-up. Patients who responded early to treatment were more likely to achieve deep remission within 2 years, which was in turn associated with deep remission at last follow-up. Elderly patients faced higher risks of hospitalization and major adverse clinical outcomes, but not of cancer or serious adverse events, suggesting that vedolizumab can be used across different age groups without a disproportionate increase in safety risk.

Keywords: Hard outcomes; Safety; Effectiveness; Long-term observation; Vedolizumab; Disease trajectory; Elderly

DIGITAL FEATURES

Graphical abstract available for this article [https://doi.org/10.6084/m9.figshare.32569122].

Key Summary Points

Why carry out this study?
Long-term real-world data on hard clinical outcomes with vedolizumab beyond 2 years remain scarce, and elderly patients are underrepresented in existing evidence.
Elderly patients represent a growing IBD population with distinct comorbidity profiles and potentially different treatment responses compared to younger adults.
This study characterized 5-year real-world outcomes of vedolizumab in a large multicenter cohort, focusing on hard endpoints, disease trajectories, and age-specific outcomes.
What was learned from the study?
Over 5 years, major adverse clinical outcomes occurred in 29.4% of patients and surgery in 23.4%, with comparable rates between CD and UC; early response predicted deep remission within 24 months, which strongly mediated long-term remission.
Elderly patients faced higher risks of major adverse clinical outcomes and hospitalization but not of serious adverse events, supporting vedolizumab use across age groups.

INTRODUCTION

Vedolizumab was the first non-anti-tumor necrosis factor (TNF) advanced therapy approved for Crohn's disease (CD) and ulcerative colitis (UC). Building on the pivotal GEMINI program [1–3], it has become an established treatment option in inflammatory bowel disease (IBD), supported by its gut-selective mechanism of action [4] and a consistently favorable efficacy–safety profile. Real-world studies have then confirmed its effectiveness and safety across diverse patient populations [5–9]. However, most available evidence focuses on intermediate endpoints, such as clinical and endoscopic outcomes within 2 years, whereas data on hard outcomes—including

surgery, hospitalization, serious adverse events, and mortality—remain limited. Long-term observational data are essential to understand the impact of medical therapy on the natural history of IBD, including cumulative risks of disease-related complications and late adverse events, and to inform clinical decision-making [10]. Yet, data beyond 2 years of follow-up with vedolizumab are still scarce, particularly in elderly patients, who are often underrepresented in clinical trials [11] and may present distinct comorbidities, drug-related risks, and treatment responses compared to younger populations [12].

We previously reported real-world data on vedolizumab effectiveness and safety up to 24 months in the LIVE study [5]. LONG-LIVE extends these observations beyond 2 years, focusing on hard outcomes, adverse events, and treatment persistence; additionally, it explores the impact of prior biologic exposure and age on long-term outcomes, providing a comprehensive assessment of vedolizumab performance in routine care.

METHODS

This retrospective study reports long-term outcomes in patients from the LIVE cohort [5], a previously published multicenter observational study conducted across 47 centers affiliated with the Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD), which enrolled patients with CD or UC initiating vedolizumab between April 2016 and June 2017 with follow-up through June 2019. All participating centers were invited to contribute extended follow-up data; centers that agreed were included in the LONG-LIVE extension, which captured outcomes from vedolizumab initiation through July 2023 or loss to follow-up. Data were extracted from medical records and integrated with the original electronic case report forms, capturing major adverse clinical outcomes, dates, and reasons for vedolizumab discontinuation, and clinical and endoscopic activity score at the last available follow-up. Major adverse clinical outcomes included both IBD-related hard outcomes (IBD-related surgeries and non-surgical hospitalizations) and serious adverse events (SAEs). SAEs, defined as serious, treatment-emergent events distinct from IBD-related surgery and hospitalization, were further classified as fatal, oncologic, or adverse events of special interest (AESIs, defined as serious, non-fatal, non-oncologic events necessitating temporary or permanent treatment discontinuation).

Reasons for discontinuation were categorized as primary ineffectiveness, secondary ineffectiveness, adverse events, remission, or other causes; loss to follow-up was recorded separately. Clinical activity was measured using the Harvey–Bradshaw Index (HBI) for CD and partial Mayo score (PMS) for UC, while endoscopic activity was assessed with the Simple Endoscopic Score for CD (SES-CD) [13] and endoscopic Mayo subscore (eMS) [14] for UC. In accordance with the definitions adopted in the original LIVE study [5], clinical response was defined as a reduction of ≥ 3 points in HBI for CD and ≥ 2 points in PMS for UC; steroid-free clinical remission as HBI < 5 for CD and PMS < 2 for UC; endoscopic remission as SES-CD ≤ 2 for CD and eMS $= 0$ for UC; and deep remission as the combination of steroid-free clinical and endoscopic remission.

The primary endpoint was the cumulative probability of major adverse clinical outcomes, a composite endpoint was designed to capture the full spectrum of unfavorable disease-related events, encompassing both hard effectiveness outcomes and serious safety outcomes. Prespecified secondary endpoints included: (1) cumulative incidences of IBD-related surgery and non-surgical hospitalization; (2) vedolizumab persistence; and (3) incidence rates of cancer, death, and AESIs. Additional exploratory analyses were performed to assess: (1) longitudinal response group transitions, defined as progression from initial clinical response category (early, late, or non-responder) to deep remission within 24 months and at last follow-up; and (2) and comparative outcomes between elderly (≥ 65 years) and non-elderly (< 65 years) patients. Exploratory analyses are intended as hypothesis generating and their results should be interpreted with additional caution.

Time-to-event outcomes (the composite endpoint of major adverse clinical outcomes, IBD-related surgeries, and non-surgical hospitalizations) were analyzed using Kaplan–Meier curves and unadjusted Cox proportional hazards models, with Fine–Gray competing-risk regression accounting for death when considering surgery and hospitalization as separate outcomes. Time-to-event analyses on the composite endpoint of major adverse clinical outcomes and its components were conducted on the full analytic cohort regardless of vedolizumab persistence status: patients who discontinued treatment contributed follow-up time until the event or censoring, ensuring that adverse outcomes occurring in non-persistent patients were fully captured. Treatment persistence was defined as the time from vedolizumab initiation to permanent discontinuation for any reason, and was estimated using Kaplan–Meier methods. Results were presented as cumulative probabilities or incidences with 95% confidence intervals (CIs), unadjusted hazard ratios (HRs), and subdistribution HRs (sHRs) with 95% CIs. Incidence rates (IRs) of death, cancer, and AESIs were estimated using Poisson regression with generalized estimating equations, and incidence rate ratios (IRRs) compared CD and UC. To assess the potential impact of selection bias introduced by incomplete retrieval of patients from the original cohort into the long-term extension (LTE) phase, we performed an inverse probability weighting (IPW) sensitivity analysis. Briefly, separate logistic regression models were fitted for CD and UC patients to estimate the probability of inclusion in the LTE cohort based on baseline demographic and clinical characteristics. For CD, the following variables were included: age, sex, disease duration, disease location, disease behavior, perianal involvement, prior anti-TNF exposure, prior immunosuppressor use, Charlson Comorbidity Index (CCI) [15] excluding age, concomitant steroids, smoking status, clinical activity, and endoscopic activity. For UC, the model included: age, sex, disease duration, disease extent, prior anti-TNF exposure, prior immunosuppressor use, CCI excluding age, concomitant steroids, smoking status, clinical activity, and endoscopic activity. The resulting propensity scores were used to derive stabilized IPW weights, trimmed at the 1st and 99th percentiles to limit the influence of extreme values. Weighted Kaplan–Meier curves for the primary composite endpoint were then compared to unadjusted estimates to evaluate the robustness of the main analyses.

Multivariable Cox regression was performed separately for CD and UC to account for disease-specific covariate sets. Variable selection was conducted using Bootstrap LASSO (least absolute shrinkage and selection operator) Cox regression. For each of 200 bootstrap iterations, the optimal penalization parameter (lambda) was selected via tenfold cross-validation. Variables were retained for the final Cox model if their inclusion frequency across bootstrap samples exceeded 50%, ensuring selection of stable and reproducible predictors. Final HRs with 95% CIs and *P*-values were derived from a standard Cox refit on the selected variables. Multivariable Poisson regression with backward stepwise selection was performed separately for CD and UC to account for disease-specific covariate sets. Given the low number of observed events for death, cancer, and SAEs, a penalized approach such as LASSO was deemed inappropriate due to insufficient statistical power for stable variable selection; backward stepwise regression was therefore preferred as a less penalized strategy, offering greater model parsimony while remaining feasible with sparse outcome data. Results from these models should be interpreted with caution given the limited number of events. Collinearity among candidate predictors was assessed prior to modeling via Pearson correlation and variance inflation factors. Adjusted estimates were presented as IRRs with 95% CIs. Baseline missing data were handled using multiple imputation by chained equations (MICE; 10 imputed datasets, pooled using Rubin's rules). Loss to follow-up was handled with non-responder imputation for the primary endpoint, as a conservative approach to mitigate the potential impact of informative censoring.

For response group transitions, patients were classified according to their initial clinical response to vedolizumab as early responders (clinical response within 14 weeks), late responders (between 14 weeks and 6 months),

or non-responders. The analysis examined transitions across three sequential states: initial response group, an intermediate landmark (achievement of deep remission at any timepoint within 24 months), and a final state (deep remission at last endoscopic follow-up, defined as the most recent endoscopic assessment available for each patient beyond 24 months). According to the original LIVE Study protocol, endoscopic assessments were captured at all available timepoints throughout the observation period of 24 months; deep remission "within 24 months" was defined as achievement of deep remission at any endoscopic assessment performed up to 24 months from vedolizumab initiation, irrespective of the specific scheduling at each center; patients without an available endoscopic assessment within 24 months were handled with non-responder imputation. For the LONG-LIVE observation, all patients still receiving vedolizumab had at least one endoscopic assessment available beyond the 24 months timepoint. Patients who discontinued vedolizumab were classified as not in deep remission at all subsequent timepoints regardless of their actual remission status after discontinuation, as the analysis aimed to capture deep remission achieved under vedolizumab treatment. Two sensitivity analyses for deep remission endpoints were performed: the first restricted the analysis to patients with at least one endoscopic evaluation available within 24 months, and the second employed MICE-based imputation (10 imputed datasets, pooled using Rubin's rules) for missing landmark status; both aimed to assess the influence of the non-responder imputation approach on the primary results. Pairwise associations between initial response groups and each outcome were assessed using logistic regression [odds ratios (ORs) with 95% CIs]. Causal mediation analysis was then performed to estimate the extent to which the effect of initial response group on the attainment of deep remission at last endoscopic evaluation was mediated through the attainment of deep remission within 24 months, quantifying the average causal mediation effect (ACME, indirect effect) and the average direct effect (ADE), each with 95% CIs and bootstrapped *P* values (1000 simulations).

Comparative analyses by age [elderly (≥ 65 years) vs. non-elderly (< 65 years)] were performed using IPW derived from propensity scores calculated separately for CD and UC (to allow the inclusion of different covariates in the propensity score model). Propensity models for CD included sex, disease duration, disease location, disease behavior, CCI excluding age, prior exposure to anti-TNF agents, and prior exposure to immunosuppressants, while, for UC, they included sex, disease duration, disease extent, CCI excluding age, prior exposure to anti-TNF agents, and prior exposure to immunosuppressants. Stabilized weights were trimmed at the 1st and 99th percentiles. Balance was evaluated with absolute standardized mean differences (SMD: < 0.1 optimal, 0.1–0.2 adequate). Weighted Kaplan–Meier, Fine–Gray, and Cox and Poisson regression analyses followed the same approach as unweighted analyses.

To evaluate the potential impact of selection bias due to incomplete follow-up retrieval of patients from the original LIVE cohort, an IPW sensitivity analysis was performed. Separate logistic regression models were fitted for CD and UC to estimate the probability of inclusion in the LONG-LIVE extension cohort based on baseline demographic and clinical characteristics; the resulting propensity scores were used to derive stabilized IPW weights, trimmed at the 1st and 99th percentiles. Weights were applied to the 782 patients with available long-term follow-up data, but outcomes for the 329 non-included patients were not imputed; this sensitivity aimed only to correct for the differential representation of patient profiles in the extension cohort. Weighted cumulative incidence estimates of the primary endpoint were then compared to unadjusted estimates to evaluate the robustness of the primary analyses against selection bias.

Statistical significance was set at two-sided $P < 0.05$ for the primary endpoint, with Holm-adjusted *P* values for secondary outcomes. Analyses were performed using SPSS 29.0.1.0 and R (RStudio 2025.5.0.496).

Ethics

The study protocol was approved on 4 June 2018 by the Ethics Committee of the coordinating center (Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy – Protocol number 18951/18, ID 2067). Independent participating centers obtained acknowledgment from their respective local Ethics Committees, which reviewed study documentation for compliance with institutional policies and data protection regulations, as per national requirements for observational retrospective studies. Patients included in the study provided written informed consent for their clinical data to be used for research purposes. The LIVE study and its LONG-LIVE extension were conducted in accordance with the Declaration of Helsinki and applicable national regulations.

RESULTS

Of the 1111 patients enrolled in the LIVE study, long-term data for the LONG-LIVE extension were available for 782 individuals (50.4% CD and 49.6% UC), with a slight male predominance ($n=447$, 57.2%); consistent with the original cohort, most patients ($n=597$, 76.3%) had prior exposure to anti-TNF therapy. Baseline characteristics are summarized in Table 1. Cumulative follow-up was 4324.1 patient-years (PY;¢ 227.9 for CD and 2096.2 for UC, $p=0.021$).

Primary Outcome

Across the entire observation, 246 patients experienced at least one major adverse clinical outcome, with Kaplan–Meier estimates of 9.7% (95% CI 7.6–11.7%) at 1 year, and 29.4% (26.1–32.7%) at 5 years. On unadjusted comparison, no statistically significant difference between CD and UC (HR 0.80, 95% CI 0.63–1.03; $P=0.090$), or by prior biologic exposure within either disease subgroup [CD: HR 0.84 (0.55–1.27), $P=0.406$; UC: HR 1.21 (0.79–1.86), $P=0.384$] were observed. Cumulative probability curves are shown in Fig. 1, with cumulative probabilities reported in Supplementary Table 1. In multivariable Cox regression with Bootstrap LASSO variable selection, in CD penetrating behavior was associated with higher risk compared to inflammatory behavior [aHR 1.77 (1.05–2.98), $P=0.031$], and stricturing behavior showed a borderline association [aHR 1.54 (1.00–2.38), $P=0.051$]; colonic location was associated with lower risk of primary endpoint compared to isolated ileal disease [aHR 0.51 (0.26–0.99), $P=0.046$]. In UC, elderly age [aHR 1.99 (1.28–3.10), $P=0.002$] and CCI excluding age [aHR 1.27 [1.01–1.59), $P=0.043$] independently predicted major adverse clinical outcome. Selected covariates and bootstrap inclusion frequencies are listed in Supplementary Table 2.

An IPW sensitivity analysis was performed to evaluate the potential impact of selection bias due to incomplete follow-up retrieval. Propensity score models showed moderate discriminative ability, indicating that observed baseline differences between included and excluded patients were limited; stabilized IPW showed adequate balance in both disease groups. After IPW, cumulative incidence estimates of major adverse clinical outcomes remained virtually identical to unadjusted analyses at all timepoints in both CD (1-year: 10.6% vs. 10.3%; 3-year: 26.2% vs. 25.9%; 5-year: 32.5% vs. 32.2%) and UC (1-year: 9.0% vs. 9.1%; 3-year: 22.1% vs. 22.1%; 5-year: 26.7% vs. 26.6%), supporting the robustness of the primary results against selection bias (Supplementary Fig. 1).

Surgical and Non-surgical Hospitalizations

During follow-up, 153 patients (19.6%) underwent at least one IBD-related surgery. Specifically, surgery occurred in 83 patients with CD (21.1%) and 70 patients with UC (18.0%); among patients with CD, 13 underwent multiple procedures. In patients with CD, all surgical procedures were performed for medically refractory disease; among patients with UC, 8 of 70 colectomies (11.4%) were performed for dysplasia, with the remainder for medically refractory disease.

Table 1 Characteristics of patients at baseline

	Inclusion in the LIVE study
Patients, *n*	782
CD *n* (%)	394
UC *n* (%)	388
Female *n* (%)	335 (42.8)
CD	177 (44.9)
UC	158 (40.7)
Age, years, mean (SD)	47.1 (15.9)
CD	45.4 (15.8)
UC	48.8 (15.8)
Over 65, *n* (%)	130 (16.6)
CD	54 (13.7)
UC	76 (19.6)
Current smokers, *n* (%)	241 (30.8)
Disease duration, years, mean (SD)	11.6 (8.8)
CD	12.8 (9.3)
UC	10.4 (7.7)
CD location, *n* (%)	
L1	111 (28.2)
L2	56 (14.2)
L3	222 (56.3)
L4	5 (1.3)
CD behavior, *n* (%)	
B1	122 (31.0)
B2	199 (50.5)
B3	73 (18.5)
CD clinical activity (HBI), *n* (%)	
Quiescent (< 5)	30 (7.6)
Mild (5–7)	102 (25.9)
Moderate (8–16)	233 (59.1)
Severe (> 16)	29 (7.4)

Table 1 continued

	Inclusion in the LIVE study
CD endoscopic activity (SES-CD), *n* (%)	
Quiescent (0–2)	10 (2.5)
Mild (3–6)	58 (14.7)
Moderate (7–15)	229 (58.2)
Severe (> 15)	97 (24.6)
UC extent, *n* (%)	
E1	18 (4.6)
E2	148 (38.2)
E3	222 (57.2)
UC clinical activity (PMS), *n* (%)	
Quiescent (0–1)	10 (2.6)
Mild (2–4)	62 (16.0)
Moderate (5–7)	235 (60.6)
Severe (> 7)	81 (20.8)
UC endoscopic activity (eMS), *n* (%)	
Quiescent (0)	5 (1.3)
Mild (1)	21 (5.4)
Moderate (2)	178 (45.9)
Severe (3)	184 (47.4)
Previous exposure to anti-TNF, *n* (%)	597 (76.3)
CD	321 (81.5)
UC	276 (71.1)
Previous cancer diagnosis, *n* (%)	61 (7.8)
Concomitant therapies, *n* (%)	
5-ASA	324 (41.1)
IMM	38 (4.9)
5-ASA + IMM	39 (5.0)
Baseline steroid therapy, *n* (%)	358 (45.8)
CD	164 (41.6)
UC	195 (50.0)

Table 1 continued

	Inclusion in the LIVE study
CRP, mg/L, mean (SD)	11.6 (16.5)
Patients with comorbidities, *n* (%)	267 (34.1)
Charlson score in patients with comorbidities, mean (SD)	2.9 (1.5)
Charlson score without age in patients with comorbidities, mean (SD)	1.5 (0.9)

CD Crohn's disease, *CRP* C-reactive protein, *eMS* endoscopic Mayo subscore, *HBI* Harvey–Bradshaw Index, *IMM* immunosuppressor, *PMS* partial Mayo score, *SD* standard deviation, *SES-CD* simple endoscopic score for CD, *TNF* tumor necrosis factor, *UC* ulcerative colitis, *5-ASA* aminosalicylates

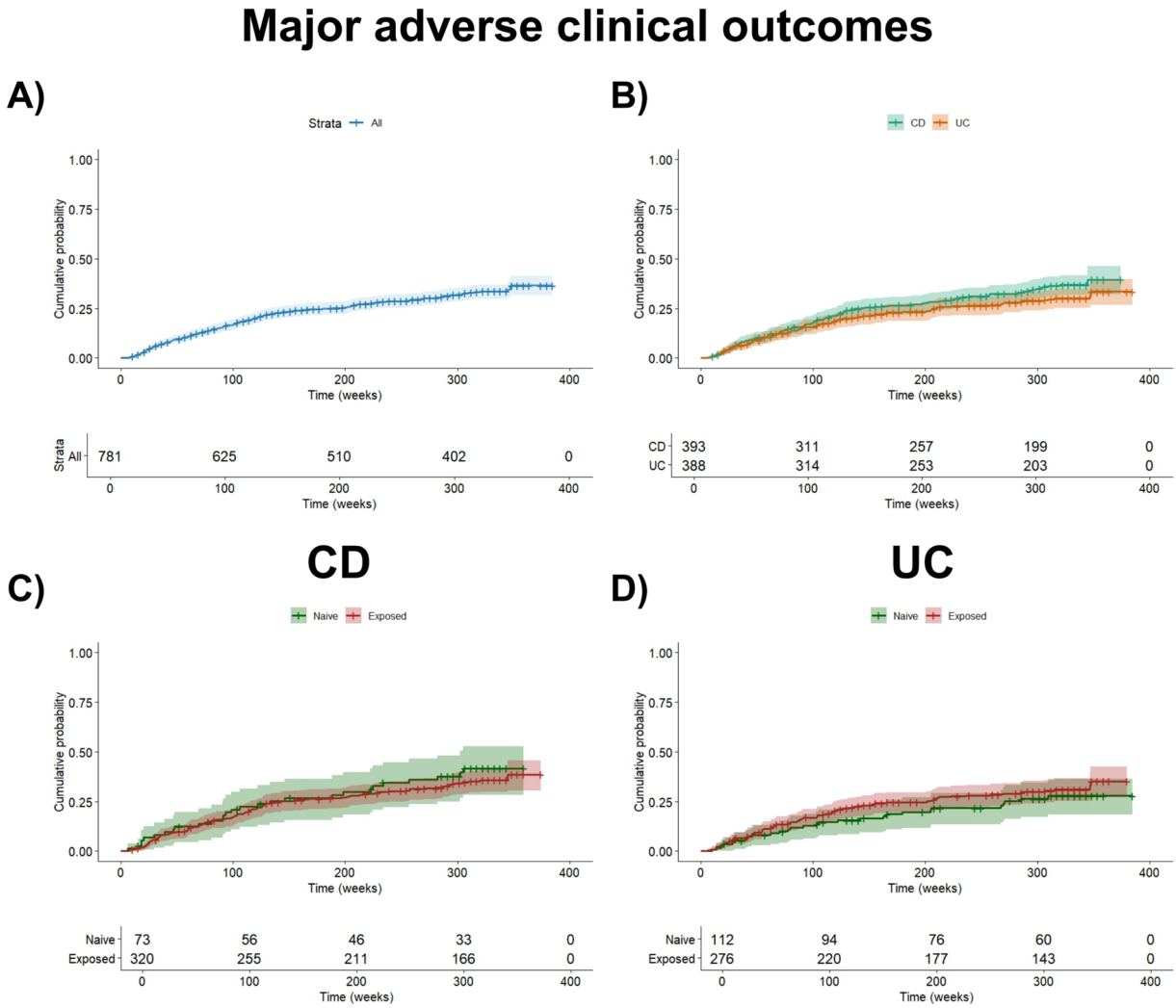


Fig. 1 Major adverse clinical outcomes. Kaplan–Meier curves showing cumulative probabilities of major adverse clinical outcomes up to the last observation. **A** Entire cohort; **B** by disease (Crohn's disease vs. ulcerative colitis); **C** Crohn's disease by prior anti-TNF exposure; **D** ulcerative colitis by prior anti-TNF exposure

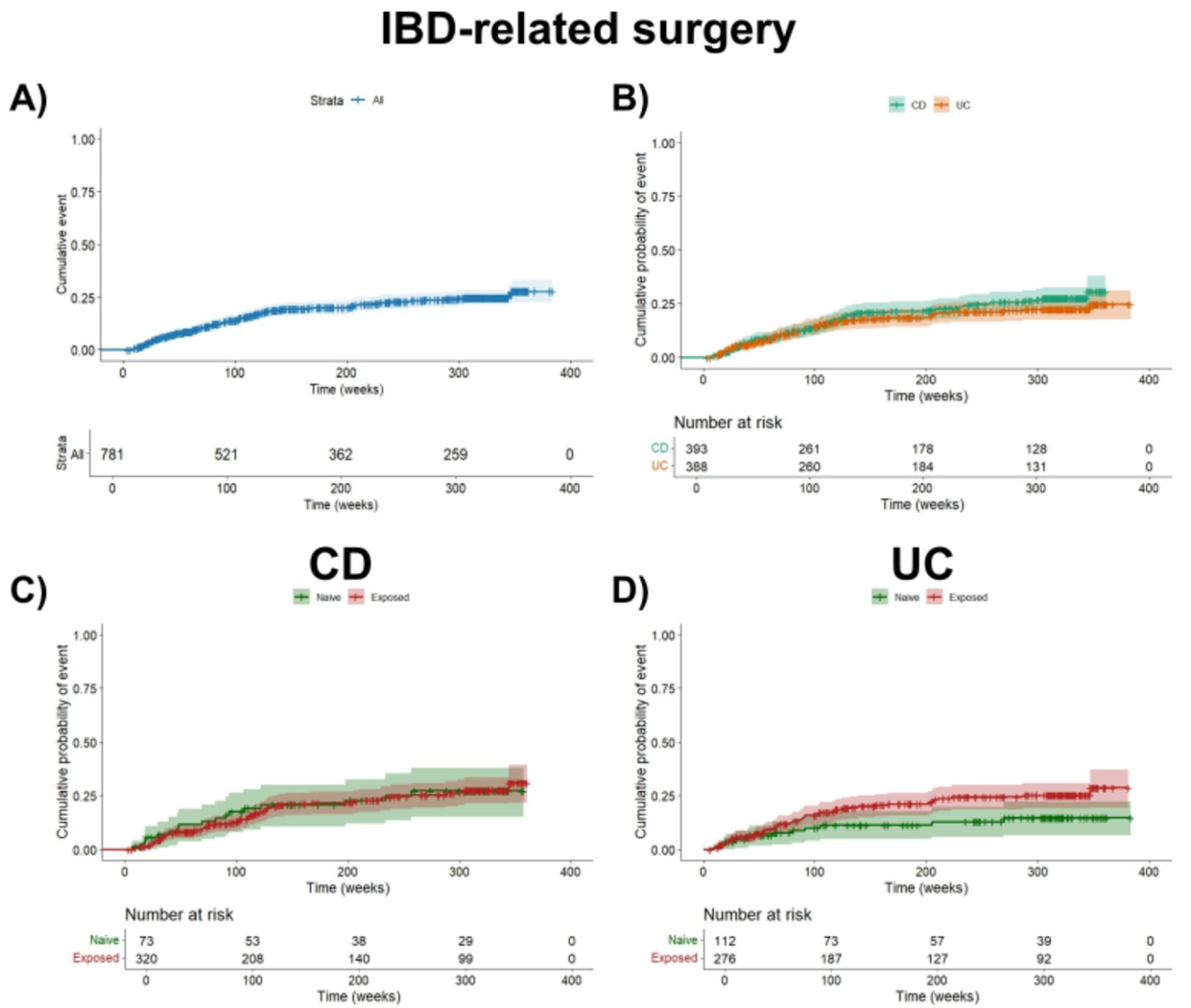


Fig. 2 Probability of IBD-related surgery. Fine–Gray curves showing cumulative probability of surgery up to the last observation. **A** Entire cohort; **B** by disease (Crohn's disease vs. ulcerative colitis); **C** Crohn's disease by prior anti-TNF exposure; **D** ulcerative colitis by prior anti-TNF exposure

Competing risk-adjusted cumulative incidences were 8.1% (95% CI 6.1–10.0%) at 1 year, and 23.4% (19.9–26.8%) at 5 years. The risk of IBD-related surgery did not differ statistically between patients with UC and patients with CD (sHR 1.19, 95% CI 0.87–1.64; $P=0.278$). When stratifying by prior biologic exposure, no statistically significant differences emerged in CD [sHR 0.95 (0.56–1.61), $P=0.862$] nor UC [sHR 1.79 (0.98–3.23), $P=0.059$] (Fig. 2). In multivariable Cox regression with Bootstrap LASSO variable selection, no stable independent predictors of surgery were identified in CD, although colonic location showed a borderline association with lower surgical risk compared to isolated ileal location [aHR 0.39 (0.15–1.01), $P=0.052$]. In UC, prior biologic exposure was associated with IBD-related surgery [aHR 2.15 (1.15–4.00), $P=0.017$].

Non-surgical hospitalizations occurred in 85 patients (10.9%). Specifically, 54 patients with CD (13.7%) and 31 patients with UC (8.0%) experienced at least one hospitalization; furthermore, 16 patients (10 CD, 6 UC) received multiple hospitalizations. Competing risk-adjusted cumulative incidences were 2.5% (1.3–3.6%) at 1 year, and 14.3% (11.2–18.5%) at 5 years.

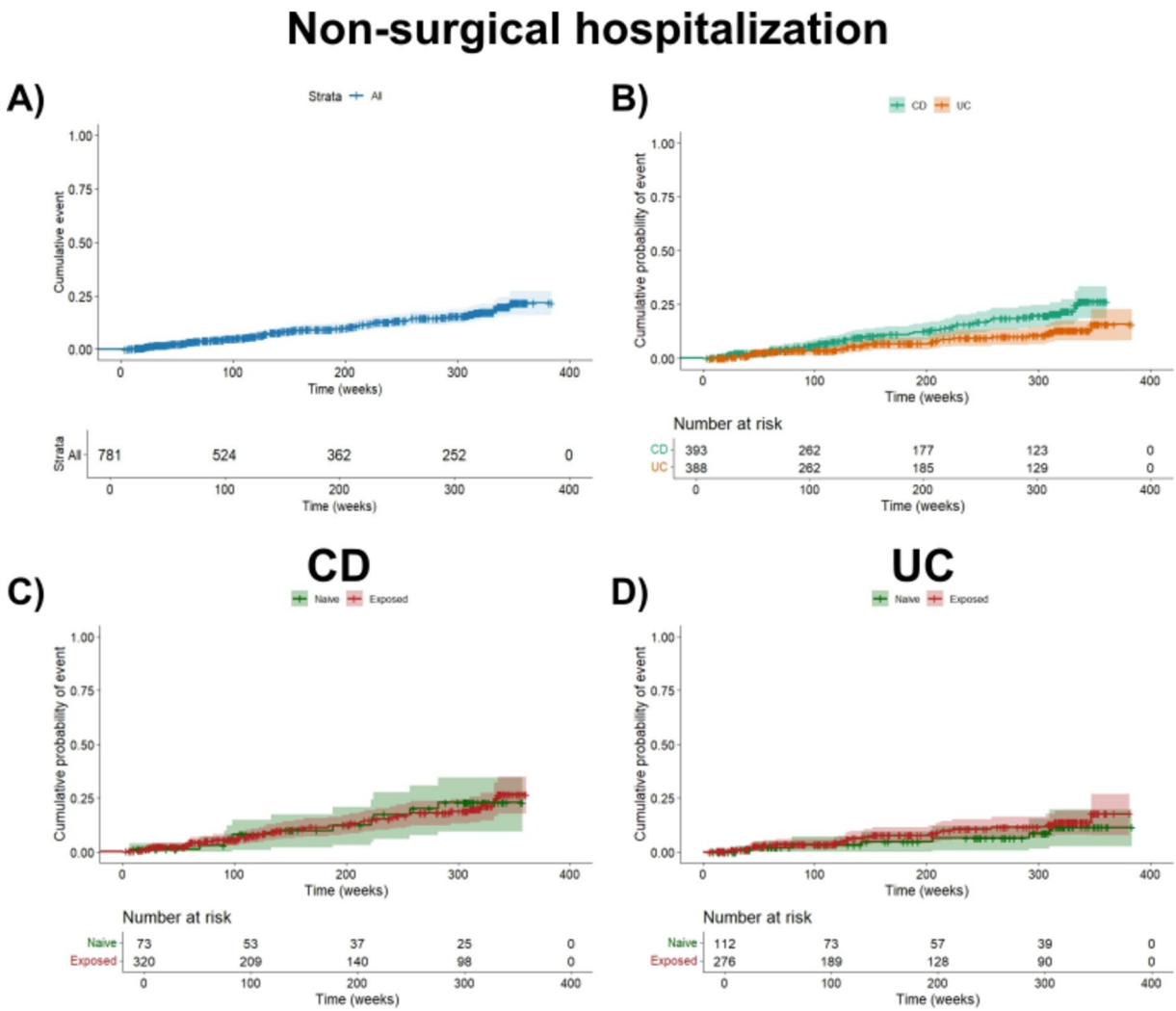


Fig. 3 Probability of non-surgical hospitalization. Fine–Gray curves showing cumulative probability of non-surgical hospitalization up to the last observation. **A** Entire cohort; **B** by disease (Crohn's disease vs. ulcerative colitis); **C** Crohn's disease by prior anti-TNF exposure; **D** ulcerative colitis by prior anti-TNF exposure

Patients with CD received more hospitalizations than patients with UC [sHR 1.80 (1.14–2.77), $P=0.011$]. No differences by prior biologic exposure were observed within disease subgroups [CD: sHR 0.94 (0.48–1.82), $p=0.855$; UC: sHR 1.41 (0.61–3.33), $P=0.419$] (Fig. 3). In multivariable Cox regression with Bootstrap LASSO variable selection, in CD elderly age predicted hospitalization [aHR 2.76 (1.50–5.08), $P=0.001$]. In UC, elderly age predicted hospitalization [aHR 3.17 (1.48–6.82), $P=0.003$] and CCI excluding age showed borderline association [aHR 1.45 (0.99–2.12), $P=0.057$]. Full cumulative probabilities and selected covariates and bootstrap inclusion frequencies are listed in Supplementary Tables 1 and 2.

Safety

A total of 17 deaths [2.2%, 8/394 (2.0%) in CD and 9/388 (2.3%) in UC] were recorded after a

Table 2 Summary of serious adverse events (SAEs): deaths (rows 1–6), oncological SAEs (rows 7–15), and adverse events of special interest (AESIs; rows 17–22). Percentages are calculated within each adverse event subtype

Fatal SAEs—causes of death (n = 17)	
Cardiovascular, *n* (%)	6 (35.3)
Infections, *n* (%)	5 (29.4)
Cancer, *n* (%)	3 (17.6)
Other, *n* (%)	2 (11.8)
Unknown, *n* (%)	1 (5.9)
Oncological SAEs (n = 17)	
Gastrointestinal, *n* (%)	4 (23.5)
Skin, *n* (%)	2 (11.8)
Breast, *n* (%)	3 (17.6)
Kidney, *n* (%)	1 (5.9)
Gynecological (non-breast), *n* (%)	3 (17.6)
Multiple myeloma, *n* (%)	1 (5.9)
Prostate, *n* (%)	2 (11.8)
Seminoma, *n* (%)	1 (5.9)
AESIs (n = 20)	
Infections, *n* (%)	10 (50.0)
Drug-related adverse event, *n* (%)	3 (15.0)
Arthralgia/arthritis, *n* (%)	2 (10.0)
Cardiovascular, *n* (%)	2 (10.0)
Other, *n* (%)	3 (15.0)

median of 28.0 months (range 10.5–70.5) from vedolizumab initiation (6 in patients who had received vedolizumab within the preceding 4 months, while the remaining 11 had discontinued it earlier), mostly due to cardiovascular disease ($n=6$) (Table 2). The overall IR of death was 3.93 per 1000 PY (95% CI 2.45–6.35), with no statistically significant difference between CD and UC [3.61 (1.80–7.21) vs. 4.31 (2.24–8.29) per 1000 PY; IRR 0.84 (0.32–2.17), $P=0.71$]. In Poisson regression, elderly age was independently associated with an increased risk of death in both CD [IRR 5.11 (1.22–21.41), $P=0.026$] and UC [IRR 34.60 (4.32–277.22), $P<0.001$].

A total of 17 new or recurrent neoplasms [2.2%, 7/394 (1.8%) in CD and 10 (2.5%) in UC] were diagnosed after a median of 41.3 months (range 3.0–71.3) from vedolizumab initiation, with gynecologic ($n=6$) and gastrointestinal ($n=4$) tumors as the most frequent (Table 2). The IR of neoplasms was 3.93 per 1000 PY (2.45–6.35), with no statistically significant difference by disease [CD: IR 3.16 (1.50–6.62) vs. UC: IR 4.79 (2.58–8.91) per 1000 PY; IRR 0.66 (0.25–1.74), $P=0.40$]. Disease duration [IRR 1.11 (1.03–1.19), $P=0.006$] and CCI excluding age [IRR 1.73 (1.17–2.54), $P=0.005$] were identified as independent predictors in CD and UC, respectively.

A total of 20 AESIs were reported, mostly infections ($n=10$, six respiratory; Table 2), with an IR of 6.27 per 1000 PY (4.30–9.14); no difference between CD and UC was observed [6.28 (3.11–10.55) vs. 2.86 (1.05–5.65) per 1000 PY; IRR 2.20 (0.84–5.71), $P=0.11$]. No independent predictors of AESIs were identified. Covariates retained in stepwise selections are listed in Supplementary Table 3.

Treatment Persistence and Outcomes at Last Follow-Up

During the observation, 529 patients (67.6%) suspended vedolizumab (272 CD, 257 UC). One-year and five-year persistence were 77.4% (95% CI 74.5–80.4%) and 38.7% (95% CI 35.4–42.3%), respectively. At unadjusted comparison, no differences between CD and UC emerged (HR 0.91, 95% CI 0.76–1.08, $P=0.265$); among patients with CD, exposed patients had significantly higher likelihood of vedolizumab discontinuation compared to naïve (HR 1.39, 95% CI 1.00–1.92, $P=0.049$), while no difference was observed in patients with UC (HR 1.06, 95% CI 0.81–1.39, $P=0.669$). Survival curves are shown in Fig. 4 and persistence estimates are provided in Supplementary Table 4. The most common reason for discontinuation was lack of

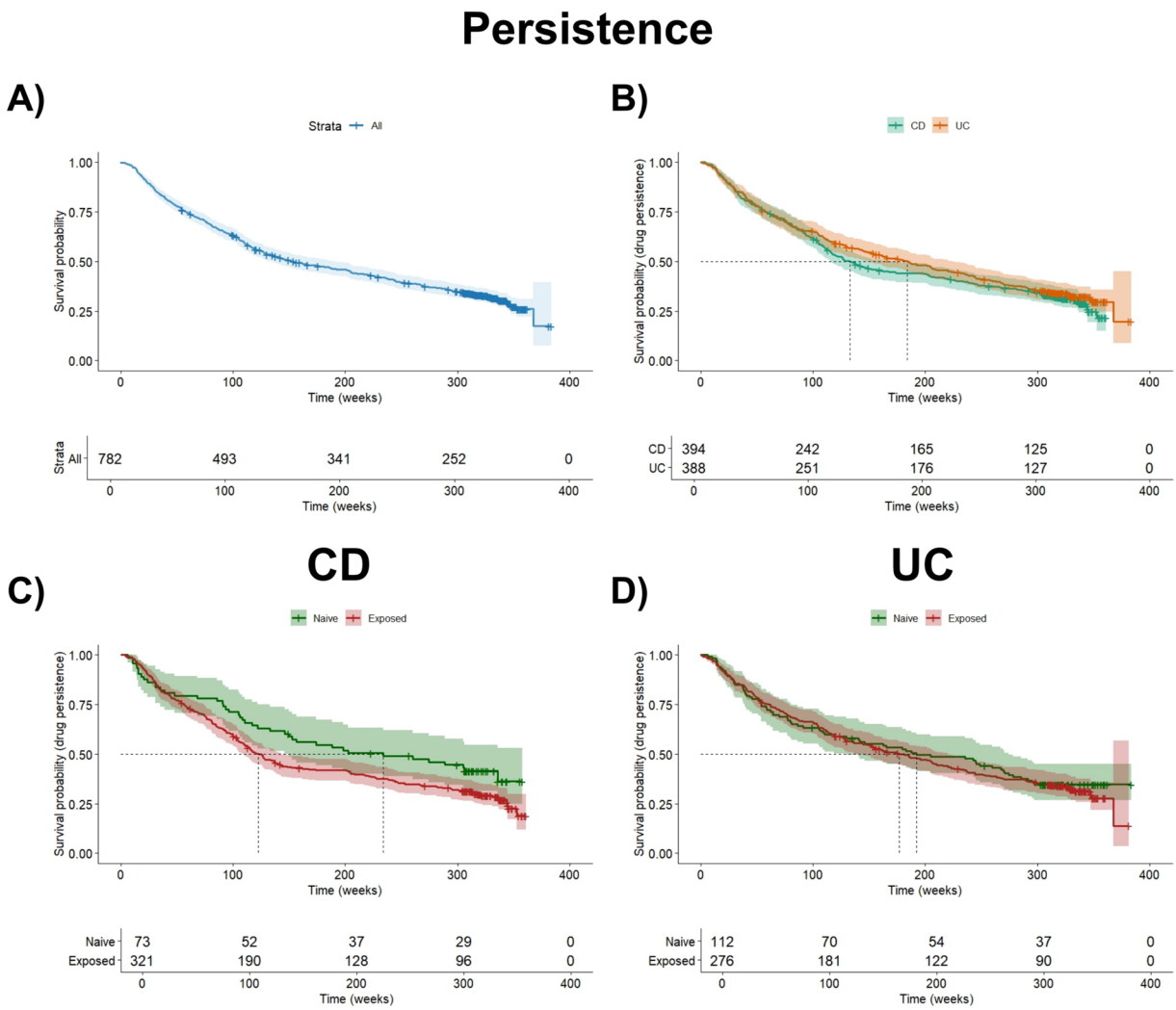


Fig. 4 Treatment persistence. Kaplan–Meier curves showing cumulative probabilities of treatment persistence up to the last observation. **A** Entire cohort; **B** by disease (Crohn's disease vs. ulcerative colitis); **C** Crohn's disease by prior anti-TNF exposure; **D** ulcerative colitis by prior anti-TNF exposure

effectiveness on intestinal symptoms ($n=423$, 80.0% of reasons for discontinuation) and 18 (3.4%) patients were lost to follow-up (cumulative vedolizumab exposure 2825.0 PY: 1403.3 for CD and 1421.7 for UC, $P=0.549$). The full list of discontinuation reasons is provided in Supplementary Table 5.

At last follow-up, 59/394 patients with CD (15.0%) and 62/388 patients with UC (16.0%) were in deep remission while still receiving vedolizumab. Early clinical responders were more likely to achieve deep remission within 24 months compared to non-responders in both CD (OR 2.71, 95% CI 1.30–6.22, $P=0.012$) and UC (OR 10.43, 95% CI 3.75–43.38, $P<0.001$), while differences between late and non-responders were not statistically significant (Supplementary Table 6). Achieving deep remission within 24 months was associated with deep remission at the last available endoscopic evaluation (CD: OR 4.81, 95% CI 2.38–9.57, $P<0.001$; UC: OR 3.00, 95% CI 1.67–5.33, $P<0.001$). Causal mediation analysis supported that this landmark had a statistically significant association with the effect of initial response on remission status at the

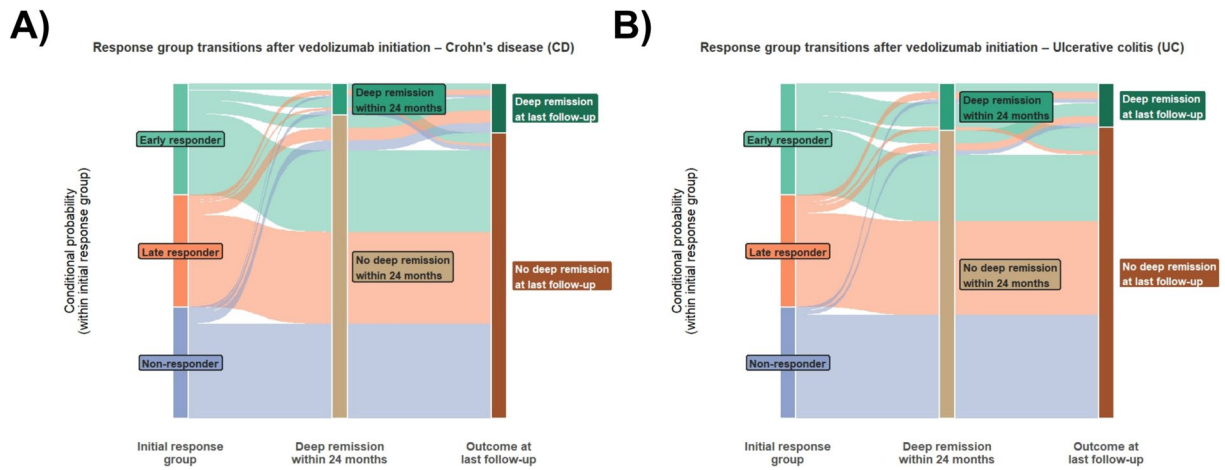


Fig. 5 Longitudinal response group transitions. Sankey diagrams showing response group transitions from initial response (early responder, late responder, non-responder) through landmark achievement (deep remission within 24 months) to final outcome (deep remission at last follow-up), stratified by disease type: Crohn's disease (*CD*, *left*) and ulcerative colitis (*UC*, *right*). Proportions are conditional on the initial response group

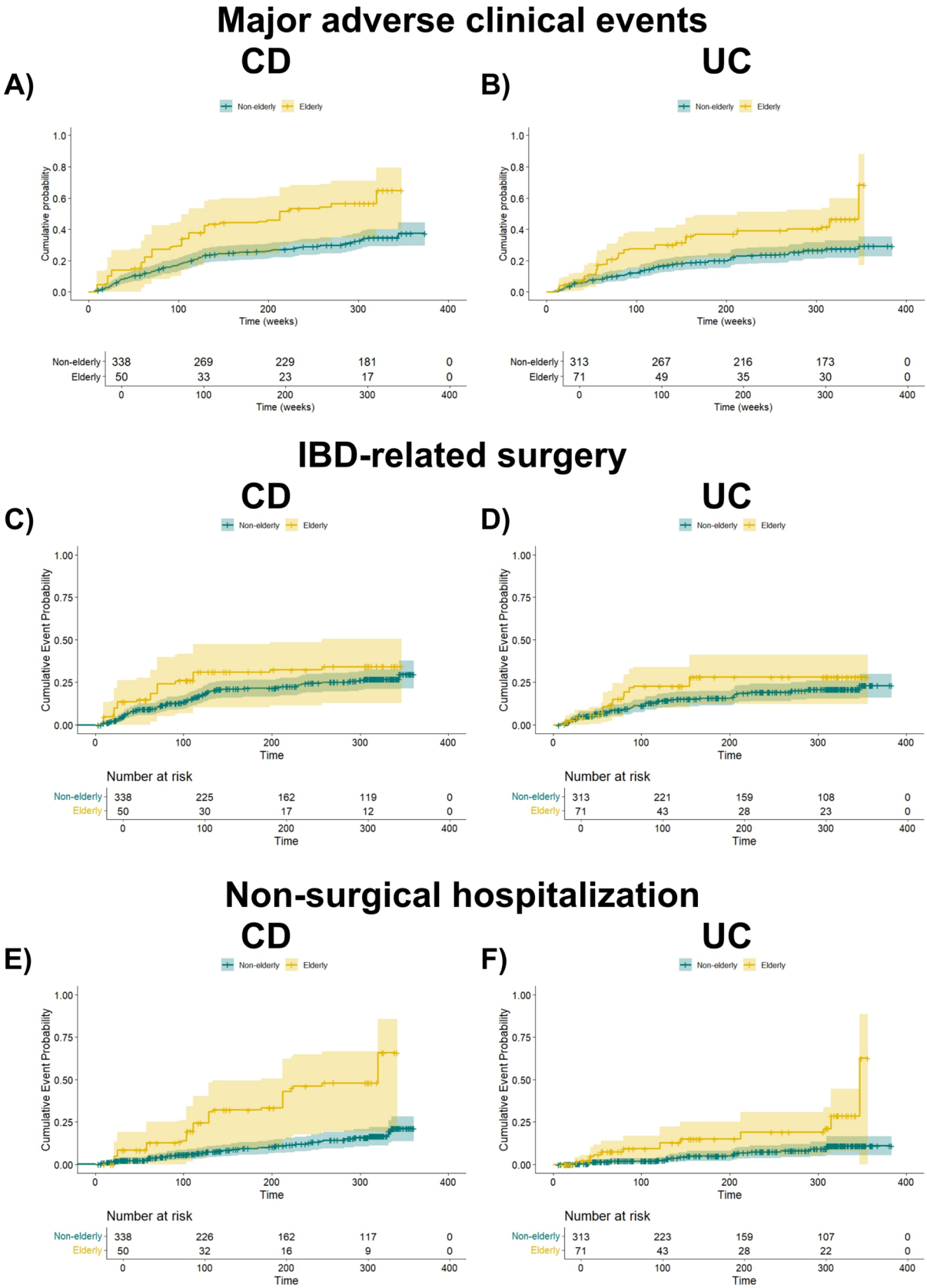
last available endoscopic evaluation (ACME: CD 0.022, 95% CI 0.003–0.049, $P=0.020$; UC 0.025, 95% CI 0.005–0.055, $P=0.004$), whereas the direct effect of initial response group was not statistically significant (ADE: CD 0.031, 95% CI –0.036–0.097, $P=0.384$; UC 0.062, 95% CI – 0.008–0.139, $P=0.088$) (Fig. 5). A sensitivity analysis restricted to patients with at least one endoscopic assessment available within 24 months (CD: $n=220$; UC: $n=278$) confirmed the robustness of the primary findings: the association between deep remission within 24 months and deep remission at last follow-up, as well as the direction and magnitude of the causal mediation estimates, remained consistent with the primary analysis. A further sensitivity analysis employing MICE-based imputation for patients with missing intermediate endoscopic follow-up yielded concordant results. Full details are reported in Supplementary Table 6.

Comparative Effectiveness and Safety in Elderly vs. Non-elderly Patients

Of the 198 elderly (≥ 65 years) patients originally enrolled in the LIVE cohort, 130 (65.7%) entered the LONG-LIVE extension. Cumulative follow-up was 3674.2 PY for the non-elderly cohort and 651.7 PY for the elderly cohort ($P<0.001$).

Baseline characteristics of the two cohorts are summarized in Supplementary Table 7. Significant differences between non-elderly and elderly patients were observed in prior exposure to immunosuppressors (CD: 74.1% vs. 44.4%, $p<0.001$; UC: 63.5% vs. 46.1%, $P=0.008$), prior exposure to anti-TNF agents (CD: 87.6% vs. 42.6%, $P<0.001$; UC: 77.6% vs. 44.7%, $P<0.001$), mean CCI excluding age (CD: 0.17 ± 0.58 vs. 0.44 ± 0.72, $P=0.002$; UC: 0.15 ± 0.56 vs. 0.37 ± 0.73, $P=0.004$), and proportion of female patients (UC: 43.9% vs. 27.6%, $P=0.014$). After IPW, optimal balance was achieved for all covariates in the CD cohort (SMD < 0.1) except for disease behavior (0.1 < SMD < 0.2, adequate balance); in the UC cohort, all covariates achieved optimal balance (SMD < 0.1). Loveplots depicting SMD before and after IPW are shown in Supplementary Fig. 2.

The cumulative probability of major adverse clinical outcomes was significantly higher in elderly versus non-elderly patients with CD (HR 2.15, 95% CI 1.34–3.47; $P=0.002$); a similar pattern was observed for patients with UC (HR 1.98, 95% CI 1.26–3.11; $P=0.003$). No differences in IBD-related surgery rates were observed in either


Major adverse clinical events
CD
UC
A)
B)
Non-elderly
Elderly
Cumulative probability
Time (weeks)
Non-elderly 338 269 229 181 0
Elderly 50 33 23 17 0
Non-elderly 313 267 216 173 0
Elderly 71 49 35 30 0
IBD-related surgery
C)
D)
Cumulative Event Probability
Time
Number at risk
Non-elderly 338 225 162 119 0
Elderly 50 30 17 12 0
Non-elderly 313 221 159 108 0
Elderly 71 43 28 23 0
Non-surgical hospitalization
E)
F)
Non-elderly 338 226 162 117 0
Elderly 50 32 16 9 0
Non-elderly 313 223 159 107 0
Elderly 71 43 28 22 0

◂**Fig. 6** Outcomes in elderly vs. non-elderly patients. Kaplan–Meier curves showing IPW-adjusted cumulative probabilities of major adverse clinical outcomes (*upper panels*), IBD-related surgery (*middle panels*), and IBD-related non-surgical hospitalization (*lower panels*) up to the last observation, stratified by age group (elderly vs. non-elderly). **A, C, E** Crohn's disease; **B, D, F** ulcerative colitis

cohort (CD: HR 1.57 [0.74–3.23), $P=0.240$; UC: HR 1.50 [0.80–2.79), $P=0.203$); younger patients, however, had a significantly higher probability of remaining free from non-surgical hospitalizations [CD: HR 4.15 (2.18–7.90), $P<0.001$; UC: HR 3.32 (1.58–6.99), $P=0.002$] (Fig. 6). Cumulative probabilities are reported in Supplementary Table 8.

In the CD cohort, no cancers occurred among elderly patients, precluding interpretation of IRR. No statistically significant differences in AESIs were observed between elderly and non-elderly patients with CD [IRR 0.67 (0.14–3.13), $P=0.609$]. In UC, no differences in cancer [IRR 1.03 (0.21–5.04), $P=0.967$] or AESIs [IRR 0.83 (0.10–6.64), $P=0.859$] were observed. Mortality was not directly compared between age groups, as isolating the effect of age would offer limited interpretative value.

DISCUSSION

In this large real-world cohort of patients with moderate-to-severe IBD—the majority refractory to prior anti-TNF therapy—we report hard clinical outcomes of vedolizumab across 4324 patient-years of follow-up.

Major adverse clinical outcomes reached a cumulative probability of 29.4% at 5 years, with no statistically significant difference between CD and UC. Disease location and behavior drove outcomes in CD—colonic location carrying lower risk and penetrating disease being associated with the highest risk—whereas, in UC, elderly age and comorbidity burden were the dominant predictors. IBD-related surgery occurred in approximately one in five patients, with comparable rates between CD and UC. Isolated colonic CD showed a borderline association with lower surgical risk; prior exposure to anti-TNF was associated with increased risk of surgery in UC. Non-surgical hospitalizations were more frequent in CD than UC, with elderly age as the strongest predictor in both diseases. Serious adverse events were uncommon throughout follow-up: mortality was 2.2%, driven predominantly by cardiovascular causes, neoplasm incidence was low, and AESIs were infrequent and mostly infectious, with infections accounting for half of all cases and respiratory infections representing the most frequent subtype. The predominance of respiratory infections among AESIs is consistent with prior evidence of an increased risk of respiratory tract infections with vedolizumab compared with other biologics [16, 17]; furthermore, previous case series reported vedolizumab-associated drug-induced pneumonitis [18]. Collectively, these observations may reflect preferential allocation of frail and comorbid patients to vedolizumab in real-world practice, incomplete gut selectivity of vedolizumab that can increase susceptibility to respiratory infections, or both.

Vedolizumab persistence declined progressively throughout the observation, with lack of effectiveness being the dominant reason for discontinuation. Early responders were more likely to achieve deep remission within 24 months compared to non-responders in both diseases, and this landmark attainment was in turn associated with deep remission at last follow-up. Causal mediation analysis suggested that the effect of initial response on long-term remission operates largely through this intermediate state, with a significant indirect effect (ACME) and a non-significant direct effect (ADE) in both CD and UC. Notably, although some patients may respond more slowly to vedolizumab—as also suggested in other work [19]—early clinical response still provides meaningful prognostic information, lying in its capacity to drive patients toward deep remission within two years.

IPW-adjusted analyses showed that elderly patients had a higher risk of overall major adverse clinical outcomes and non-surgical hospitalization in both diseases, while surgery rates and safety outcomes—including AESIs and neoplasms—did not differ between age groups.

The excess risk observed in elderly patients after covariate balancing likely reflects dimensions of biological ageing not fully captured by the Charlson Comorbidity Index (included in the IPW model), including frailty, functional reserve, and polypharmacy, factors that are relevant determinants of outcomes in older IBD patients and can inform clinical decision-making when initiating advanced therapies in this population.

Our findings are broadly consistent with previous reports, while providing extended longitudinal insights by leveraging a longer follow-up in a population enriched with refractory patients, a profile that contextualizes differences in outcome rates discussed below. Surgery incidence in our cohort was higher than in unselected incident IBD populations [20], as expected given that requirement for biological therapy already identifies patients with disease refractory to conventional treatment; the lower surgery incidence reported in the GEMINI extension study [21] may be attributed to the selection of a cohort enriched with responders from preceding trials. In CD, despite a shorter observation period, surgical rates in our cohort were broadly consistent with the 24% 10-year cumulative incidence reported in a contemporary European population-based inception cohort [22], suggesting that the higher refractoriness of our population counterbalanced the difference in follow-up duration. In UC, colectomy rates substantially exceeded those of unselected incident cohorts [23], likely reflecting the compounded effect of prior anti-TNF failure—the sole independent predictor of colectomy in our multivariable analysis—long disease duration, and older age. Consistent with published data in biologics-treated UC populations [24], refractory disease accounted for the vast majority of surgical indications, with neoplastic progression representing a minority of cases. Consistent with previous data [26], isolated colonic disease appears to be associated with a lower risk of surgery, which may be dependent on a milder disease phenotype or a more conservative surgical approach related to the less destructive nature of surgery for ileal disease [27]. In UC, previous anti-TNF exposure was the sole predictor associated with an increased risk of surgery, possibly reflecting a more treatment-refractory patient cohort. Persistence estimates align with those reported in other large real-world cohorts [9, 17]. and mirrors the pattern of lower persistence in biologic-experienced compared with naïve patients observed across advanced therapies. Anti-TNF agents, having been available for over two decades, offer the most extensive long-term real-world evidence: in patients with CD treated with infliximab or adalimumab, approximately one in four achieves sustained remission at 10-year follow-up, with surgical resection required in up to 36% and treatment discontinuation due to serious adverse events in approximately 26% [25]. A systematic review and meta-analysis including nearly 30,000 patients with CD reported 1- and 2-year vedolizumab persistence rates of 65.3% and 54.8%, respectively, with more favorable outcomes in biologic-naïve than in biologic-experienced patients; in biologic-naïve patients specifically, persistence was numerically higher with vedolizumab than with anti-TNF agents at both 1 year (84.6% vs. 75.3%) and 2 years (70.6% vs. 64.6%), though between-study heterogeneity was substantial [9]. For ustekinumab, long-term real-world persistence data are now emerging: in a Canadian nationwide patient support program including over 8700 patients with CD, persistence reached approximately 60% at 4 years, with biologic-experienced patients showing significantly lower persistence than naïve patients [28], consistent with the pattern observed across advanced therapies in refractory populations. The slightly higher incidence of AEs and neoplasms reported by Louis et al. [29] likely reflects more systematic capture inherent to their prospective design and different outcome definitions rather than a true difference in event rates. Our earlier work [30] showed reduced persistence in the elderly UC cohort and reported no difference in rates of adverse events; the present study complements these findings by demonstrating that elderly patients carry a higher burden of major adverse clinical outcomes and non-surgical hospitalizations in both CD and UC, while confirming that AESI and cancer rates remain comparable across age groups.

Strengths of this study include the large sample size with extended follow-up yielding over 4300 cumulative patient-years, the use of hard clinical endpoints, and the focused evaluation of elderly patients with IPW adjustment. The application of causal mediation analysis to formally decompose the effect of initial response on long-term outcomes represents a methodological contribution that goes beyond standard association testing, providing a framework applicable to other treatment sequences in IBD. Nevertheless, limitations must be acknowledged. First, as an observational retrospective study, not all associations should be interpreted as causal, and residual confounding remains possible despite multivariable adjustment and propensity score weighting. Of the 1111 patients enrolled in the original LIVE study, 329 (29.6%) did not enter the LONG-LIVE extension, primarily due to non-participation of their contributing centers in the long-term follow-up phase. To formally evaluate the potential impact of this incomplete retrieval on our estimates, we performed an IPW sensitivity analysis in which the probability of inclusion in the extension cohort was modeled from baseline demographic and clinical characteristics; IPW-adjusted cumulative incidence estimates of the primary endpoint were comparable to unadjusted estimates in both CD and UC, supporting the representativeness of the analyzed cohort; nevertheless, because center-level characteristics were not included in the propensity score model, between-center variability remains a potential residual source of selection bias that the IPW approach cannot fully address. Retrospective AE capture may underestimate true event frequency; additionally, the rarity of AEs in our cohort, reflected in the wide CIs, warrants further caution in interpreting the estimates. The age-stratified analysis and the response group transition and causal mediation analyses were exploratory investigations, and their results should not be interpreted as demonstrating causal effects; furthermore, the age threshold of 65 years used to define elderly patients, while consistent with prior IBD literature, represents a simplified categorization that does not fully capture the heterogeneity of biological ageing [31].

CONCLUSION

This study provides 5-year real-world data on hard clinical outcomes—IBD-related surgeries, non-surgical hospitalizations, and serious adverse events—in a large population of patients with IBD; reduction in hospitalizations and surgeries is explicitly recognized among the ultimate therapeutic goals of IBD management [32], yet these endpoints remain underreported in the literature. In our cohort, the 29.4% 5-year cumulative probability of major adverse clinical outcomes was driven primarily by IBD-related complications: approximately one in five patients underwent IBD-related surgery and 14.3% experienced non-surgical hospitalization, while SAEs remained uncommon. The variable impact of prior anti-TNF exposure across disease types and endpoints underscores the need for individualized treatment decisions. Five-year persistence of 38.7%, while an imperfect proxy of both efficacy and tolerability, adds context to the primary endpoint findings. In exploratory analyses, early attainment of deep remission within 24 months was associated with sustained remission at last follow-up, and elderly patients faced a higher burden of hospitalizations and major adverse clinical outcomes but not of SAEs, findings that carry potential relevance for prognostic stratification and treatment decisions across age groups. Future prospective research focusing on hard clinical endpoints and patient-reported outcomes—with particular attention to frailty and comorbidity burden—is needed to clarify whether early treatment optimization can modify long-term disease trajectories.

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designed the study. Giuseppe Privitera and Daniela Pugliese contributed to statistical analysis. Giuseppe Privitera wrote the original draft of the manuscript and Daniela Pugliese revised the manuscript draft. Flavia Palumbo, Fabio Salvatore Macaluso, Lucrezia Laterza, Veronica Pardi, Anna Viola, Daniele Noviello, Brigida Barberio, Chiara Ricci, Paola Balestrieri, Maria Cappello, Giovanni Maconi, Renato Sablich, Angela Variola, Raffaele Bennato, Luca Pastorelli, Laurino Grossi, Davide Giuseppe Ribaldone, Andrea Buda, Fabrizio Bossa, Antonio Di Sario, Angelo Viscido, Benedetto Neri, Giammarco Mocci, Cristiano Pagnini, Maria Beatrice Principi, Marina Coletta, Carlo Petruzzellis, Silvia Mazzuoli, Stefano Festa, Agnese Miranda, Cristina Bezzio, Libera Fanigliulo, Giulia Rocco, Elisabetta Dal Pont, Rocco Spagnuolo, Edoardo Vincenzo Savarino, Flavio Andrea Caprioli, Walter Fries, Linda Ceccarelli, Franco Scaldaferri, Ambrogio Orlando, Anna Testa contributed to data collection. Alessandro Armuzzi oversaw the project, including statistical analysis and manuscript writing, and guarantees for the integrity of the work. All authors reviewed and approved the final draft of the article before submission.

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Data Availability. Data can be made available upon request from third parties.

Declarations

Conflicts of Interest. Giuseppe Privitera received consultancy fees from Johnson and Johnson. Daniela Pugliese received speaker fees from MSD, Takeda, Galapagos, Janssen and Pfizer. Daniela Pugliese is an Editorial Board member of Advances in Therapy. Daniela Pugliese was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. Alessandro Armuzzi: consulting and/or advisory board fees from AbbVie, Amgen, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Celltrion, Eli-Lilly, Ferring, Galapagos, Gilead, Janssen, MSD, Mylan, Pfizer, Protagonist Therapeutics, Roche, Samsung Bioepis, Sandoz, Takeda; lecture and/or speaker bureau fees from AbbVie, Amgen, Arena, Biogen, Bristol-Myers Squibb, Eli-Lilly, Ferring, Galapagos, Gilead, Janssen, MSD, Mitsubishi-Tanabe, Novartis, Pfizer, Roche, Sandoz, Samsung Bioepis, Takeda; and research grants from MSD, Pfizer, Takeda and Biogen. Flavia Palumbo, Fabio Salvatore Macaluso, Lucrezia Laterza, Veronica Pardi, Anna Viola, Daniele Noviello, Brigida Barberio, Chiara Ricci, Paola Balestrieri, Maria Cappello, Giovanni Maconi, Renato Sablich, Angela Variola, Raffaele Bennato, Luca Pastorelli, Laurino Grossi, Davide Giuseppe Ribaldone, Andrea Buda, Fabrizio Bossa, Antonio Di Sario, Angelo Viscido, Benedetto Neri, Giammarco Mocci, Cristiano Pagnini, Maria Beatrice Principi, Marina Coletta, Carlo Petruzzellis, Silvia Mazzuoli, Stefano Festa, Agnese Miranda, Cristina Bezzio, Libera Fanigliulo, Giulia Rocco, Elisabetta Dal Pont, Rocco Spagnuolo, Edoardo Vincenzo Savarino, Flavio Andrea Caprioli, Walter Fries, Linda Ceccarelli, Franco Scaldaferri, Ambrogio Orlando, Anna Testa declare no competing interests.

Ethical Approval. The study protocol was approved on 4 June 2018 by the Ethics Committee of the coordinating centre (Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy – Protocol number 18951/18, ID 2067). Independent participating centers obtained acknowledgment from their respective local Ethics Committees, which reviewed study documentation for compliance with institutional policies and data protection regulations, as per national requirements for observational retrospective studies. Patients included in the study provided written informed consent for their clinical data to be used for research purposes. The LIVE study and its LONG-LIVE extension were conducted in accordance with the Declaration of Helsinki and applicable national regulations.

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