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Primary Sclerosing Cholangitis Worsens Prognosis in Patients With Inflammatory Bowel Disease: A Propensity-Matched Cohort Study

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ABSTRACT

Background: Few data are available on the impact of primary sclerosing cholangitis (PSC) on inflammatory bowel disease (IBD).

Objective: We conducted a retrospective study using TriNetX to compare the outcomes of patients with IBD and those with concomitant IBD and PSC.

Methods: All patients with a confirmed diagnosis of Crohn's disease (CD), ulcerative colitis (UC), or indeterminate colitis with or without PSC were eligible. One-to-one propensity score matching was employed to balance demographic parameters, comorbid conditions, and IBD medications between cohort 1 (IBD) and cohort 2 (IBD and concomitant PSC). The primary endpoint was a composite endpoint including the risk of mortality, hospitalization, and surgery. Risks were expressed as Hazard Ratio (HR) with a 95% confidence interval (CI).

Results: A total of 398,980 IBD patients were analyzed (cohort 1: 395,874 and cohort 2: 3106). After propensity-score-matching, 3007 patients from each group were included (mean age 48.1 ± 19.4 years, female 40%, UC 75% CD 24.8%). Approximately 1%–2% of patients were treated with advanced therapies. Cohort 2 patients had a higher risk of experiencing the composite endpoint compared to cohort 1 group (HR:1.32, 95%CI:1.23–1.42). Similarly, a higher risk of hospitalization and mortality was identified in subjects with IBD and concomitant PSC (HR:1.32, 95% CI: 1.22–1.43 and HR: 1.69, 95%CI: 1.46–1.96). Both CD and UC patients with concomitant PSC had a higher risk of achieving the composite endpoint (HR: 1.18, 95%CI: 1.02–1.37 and HR: 1.29, 95%CI: 1.18–1.40). An increased risk of mortality and hospitalization was found both in patients with CD (HR: 2.16, 95%CI:1.58–2.95, and 1.20, 95%CI:1.03–1.41) and UC (HR: 1.87, 95%CI: 1.57–2.22 and HR: 1.27, 95%CI:1.16–1.40) and concomitant PSC.

Conclusion: In this administrative study of patients with IBD and PSC, concomitant PSC was associated with an increased risk of mortality and hospitalization.

1 | Introduction

Inflammatory bowel diseases (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), are chronic and disabling immune-mediated diseases of the gastrointestinal tract, with an increasing incidence worldwide [1, 2]. Besides affecting the gastrointestinal tract, IBD can involve extraintestinal manifestations, that can significantly impact the quality of life of IBD patients [3, 4]. Primary sclerosing cholangitis (PSC) is a chronic liver disease marked by inflammation and fibrosis of the bile ducts, which substantially raises the risk of end-stage liver disease, cancer, and mortality [5]. The incidence and prevalence of PSC vary significantly by region. In Northern Europe, the incidence is 1.58 per 100,000 individuals, and the prevalence is 32 per 100,000, with an upward trend in recent years [6, 7]. Genetic and environmental factors significantly contribute to the onset of the disease, and the intestinal microbiome is increasingly believed to play a pathogenic role. Up to 70% of PSC patients have a concomitant IBD [5]. Similarly, PSC is notably more prevalent in IBD patients compared with the general population, with prevalence data reaching 8% of the IBD population [8–11]. In patients with UC, several independent risk factors for PSC were identified, including male sex (95% CI, OR 2.77, $p = 0.022$), pancolitis (95% CI, OR 2.85, $p = 0.011$), nonsmoking status at diagnosis (95% CI, OR 9.25, $p = 0.03$), and history of appendectomy (95% CI, OR 4.11, $p = 0.019$) [10].

Although the association between IBD and PSC is well-documented, the impact of PSC on the prognosis of IBD patients is not fully understood. Currently, there are no studies on this topic with a long follow-up or with a sufficiently large sample size to evaluate this association. To bridge this knowledge gap, we conducted a retrospective cohort study using TriNetX, a multi-institutional database, to compare the outcomes of patients with IBD to those with both IBD and concomitant PSC, from 2003 to 2023. We investigated the risks of mortality, hospitalization, and surgery, providing comprehensive insights into the prognostic implications of PSC in IBD patients.

2 | Methods

2.1 | Study Design

This was a non-interventional, retrospective study conducted with data obtained from TriNetX LLC ("TriNetX"). TriNetX is a global federated health research network that provides access to electronic medical records (EMRs) from healthcare organizations (HCOs) worldwide [12]. The analysis was conducted with the TriNetX Global Collaborative Network, which provides access to data containing diagnoses, procedures, medications, laboratory values, and genomic information from approximately 130 million patients from 108 HCOs from around the world. TriNetX data is updated periodically asynchronously and has been used to run multiple studies on IBD published in several peer-reviewed scientific journals [13–15]. Data collection, processing, and transmission were performed in compliance with the data protection laws of each contributing HCO. The Global Collaborative Networks is a distributed network, and analytics are performed on anonymized or pseudonymized/de-identified (per HIPAA) data stored at the HCOs, with only aggregate results being returned to the TriNetX platform. TriNetX is ISO 27001:2013 certified and maintains a robust IT security program that protects personal and health care data [12].

2.2 | Study Population

A real-time search and analysis of the Global Collaborative Network in the TriNetX platform was conducted from 2003 to 2023. The study identified patients based on specific ICD-10-CM codes corresponding to their diagnoses. All patients with a confirmed diagnosis of Crohn's disease (CD) [ICD-10-CM: K50], ulcerative colitis (UC) [ICD-10-CM: K51], or indeterminate colitis [ICD-10-CM: K52.3], with or without concomitant primary sclerosing cholangitis (PSC) [ICD-10-CM: K83.01] or cholangitis [ICD-10-CM: K83.0], were eligible for inclusion in the study. The analysis included outcomes that occurred in the time window that started 1 day after the first occurrence of the index event (diagnosis of IBD) and ended 3650 days after the first occurrence of the index event. We identified two cohorts for comparison: cohort 1 comprised patients with IBD alone, while cohort 2 comprised patients with both IBD and concomitant PSC. To ensure comparability between the cohorts, we utilized one-to-one propensity score matching, balancing demographic parameters, comorbid conditions, and IBD medications between the two groups. Particularly, propensity score matching was performed on 12 characteristics. In the demographic category, patients were matched on age at index, male, female, white, black, or African American, Asian, or other race characteristics. In the diagnosis category, patients were matched on ulcerative colitis, Crohn's disease, liver transplant status, and nicotine dependence characteristics.

2.3 | Study Outcomes

The primary endpoint of the study was a composite endpoint encompassing the risk of mortality, hospitalization, and colectomy surgery 10 years after the IBD diagnosis. Secondary endpoints included individual risks of mortality, colectomy surgery (and perianal surgery in CD), and hospitalization. Upon completion of propensity score matching, we analyzed the incidence rates of the primary and secondary endpoints in both cohorts. Statistical analyses were performed to elucidate the impact of concomitant PSC on the prognosis of patients with IBD.

2.4 | Statistical Analysis

All analyses were generated with TriNetX platform software (TriNetX, Cambridge, MA) on August 7th, 2023. Baseline

Summary

Summarise the established knowledge on this subject

- Up to 8% of patients with inflammatory bowel disease (IBD) experience concomitant primary sclerosing cholangitis (PSC)
- The prognosis of patients with IBD and concomitant PSC is unknown.

What are the significant and/or new findings of this study?

- Patients with IBD and concomitant primary sclerosing cholangitis have an increased risk of mortality and hospitalization.
- The increased risk of negative outcomes in patients with IBD and concomitant PSC highlights the need to closely monitor these patients.

characteristics of cohorts were described using means and standard deviations when numerical and patient count and proportions when categorical. To assess the difference in significance between them, *t* test and X^2 test were used for numeric and categorical characteristics, respectively. The *p* value threshold for significance was 0.05. The compare outcomes analytic included survival analysis. Risk difference, risk ratio and odds ratio were calculated. Risks were expressed as Hazard Ratios (HR) with corresponding 95% confidence intervals (CI). Regarding survival analysis, the Kaplan-Meier analysis was employed to evaluate the probability of the outcome. Median survival, survival probability at the end of the time window, log-rank test, Hazard Ratio and test for proportionality were assessed. The statistical methodologies and software suites employed in generating statistical analyses encompass the following: Java 11.0.16 (including Apache Commons Math 3.6.1), *R* 4.0.2 (with Hmisc1-1 and Survival 3.2–3), and Python 3.7 (utilizing lifelines 0.22.4, matplotlib 3.5.1, numpy 1.21.5, pandas 1.3.5, scipy 1.7.3, and statsmodels 0.13.2).

2.5 | Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki. Ethical approval and informed consent were not necessary as all data were completely anonymized.

3 | Results

3.1 | Baseline Characteristics

As shown in Table 1 and Supporting Information S1: Table 1, a total of 398,980 patients were identified, particularly patients with IBD (cohort 1: 395,874 patients) and with IBD plus PSC (cohort 2: 3106 patients). Before matching, significant differences were observed in gender distribution, IBD type, liver transplant status, and some medication use. These differences were appropriately addressed by matching, resulting in similar baseline characteristics between the groups. After propensity score matching, 3007 patients from each group were included (mean age 48.1 ± 19.4 years, female 40%, UC 75%, CD 24.8%).

3.2 | IBD Patients

3.2.1 | Primary Endpoint

The composite outcome, which included any mortality, hospitalization, and colectomy, was observed in 1623 patients (54.0%) in the IBD with PSC cohort and 1247 patients (41.5%) in the IBD without PSC cohort (Table 2). As shown in Figure 1, the median time to the composite outcome was significantly shorter in the IBD with PSC cohort (851 days) compared to the IBD without PSC cohort (1792 days). The log-rank test indicated a highly significant difference between the two cohorts ($p < 0.001$), with a chi-square (χ^2) value of 56.737. The hazard ratio was 1.326 (95% CI 1.232, 1.428), suggesting that patients in the IBD with PSC cohort had a 32.6% higher risk of experiencing the composite outcome compared with those in the IBD without PSC cohort.

3.2.2 | Secondary Endpoints

Mortality analysis, as shown in Figure 2., revealed significant differences between the two cohorts. Specifically, the survival probability at the end of the 10-year period was lower for patients with both IBD and PSC (70.86%) compared with those with only IBD (82.62%). The log-rank test indicated a highly significant difference in survival between the two cohorts ($p < 0.001$, χ^2 51.89). The hazard ratio was 1.69 (95% CI 1.46 −1.96), meaning that patients with IBD and PSC had a 69.7% higher risk of mortality than those with only IBD.

Hospitalization rates also differed significantly between the two cohorts. The median hospitalization-free survival time from the IBD diagnosis was shorter for patients in cohort 2 (1.40 days) compared with those in cohort 1 (2.71 days). At the end of the time window, the probability of experiencing hospitalization was 66.10% for the IBD with PSC group and 53.87% for the IBD without PSC group. The log-rank test showed a significant difference ($p < 0.001$, χ^2 48.7). The hazard ratio was 1.32 (95% CI 1.22, 1.43), indicating a 32.6% higher risk of hospitalization for patients with both conditions.

Conversely, there was no significant difference between the two groups in terms of surgery. The probability of undergoing surgery was similar in both cohorts, with 12.12% for the IBD with PSC group and 10.44% for the IBD without PSC group. The log-rank test did not indicate a significant difference ($p = 0.09$), and the hazard ratio was 1.18 (95% CI 0.97, 1.43), suggesting a non-significant increase in risk for the IBD with PSC group. Similarly, for perianal surgery, there was no significant difference in outcomes between the two cohorts. The probability of developing perianal disease by the end of the time window was 4.03% for the IBD with PSC group and 5.44% for the IBD without PSC group. The log-rank test ($p = 0.065$) and the hazard ratio (0.72, 95% CI 0.97, 1.43) both indicated that the difference was not statistically significant.

TABLE 1 | Patients charateristics after propensity score matching; Cohort 1, IBD ($N = 3007$) and cohort 2, IBD plus PSC ($N = 3007$).

	Before PSM				After PSM			
Demographics	IBD plus PSC	IBD no PSC	*p*-value	Std diff.	IBD plus PSC	IBD no PSC	*p*-value	Std diff.
N	3.106	395.874			3.007	3.007		
Age at index	48.0 +/− 19.4	49.3 +/− 20.3	< 0.001	0.067	48.1 +/− 19.4	48.1 +/− 19.7	0.984	0.001
Sex								
Female	1206 (39.90%)	213723 (55.50%)	< 0.001	0.316	1206 (40.10%)	1204 (40.00%)	0.958	0.001
Male	1796 (59.40%)	164362 (42.70%)	< 0.001	0.339	1780 (59.20%)	1780 (59.20%)	1	< 0.001
Race								
White	2141 (70.80%)	270641 (70.30%)	0.52	0.012	2131 (70.90%)	2133 (70.90%)	0.955	0.001
Black or African American	265 (8.80%)	29592 (7.70%)	0.026	0.039	260 (8.60%)	263 (8.70%)	0.891	0.004
Asian	81 (2.70%)	9949 (2.60%)	0.741	0.006	81 (2.70%)	84 (2.80%)	0.813	0.006
Other race	26 (0.90%)	4361 (1.10%)	0.158	0.027	26 (0.90%)	28 (0.90%)	0.785	0.007
Diagnosis								
Ulcerative colitis	2276 (75.30%)	208137 (54.10%)	< 0.001	0.456	2260 (75.20%)	2265 (75.30%)	0.881	0.004
Crohn's disease	747 (24.70%)	174688 (45.40%)	< 0.001	0.443	747 (24.80%)	726 (24.10%)	0.529	0.016
Indeterminate colitis	821 (27.20%)	106762 (27.70%)	0.487	0.013	821 (27.30%)	858 (28.50%)	0.288	0.027
Liver transplant status	415 (13.70%)	839 (0.20%)	< 0.001	0.55	399 (13.30%)	399 (13.30%)	1	< 0.001
Nicotine dependence	168 (5.60%)	39446 (10.20%)	< 0.001	0.174	168 (5.60%)	176 (5.90%)	0.657	0.011
Medication								
Mesalamine	648 (21.40%)	53195 (13.80%)	< 0.001	0.201	643 (21.40%)	473 (15.70%)	< 0.001	0.146
Corticosteroids for systemic use	1152 (38.10%)	146512 (38.10%)	0.948	0.001	1144 (38.00%)	1208 (40.20%)	0.091	0.044
Azathioprine	202 (6.70%)	8647 (2.20%)	< 0.001	0.216	200 (6.70%)	105 (3.50%)	< 0.001	0.144
Methotrexate	17 (0.60%)	6014 (1.60%)	< 0.001	0.098	17 (0.60%)	41 (1.40%)	0.002	0.082
Tacrolimus	308 (10.20%)	4059 (1.10%)	< 0.001	0.405	298 (9.90%)	264 (8.80%)	0.132	0.039
Infliximab	39 (1.30%)	7081 (1.80%)	0.025	0.044	39 (1.30%)	30 (1.00%)	0.276	0.028
Adalimumab	54 (1.80%)	8683 (2.30%)	0.084	0.033	54 (1.80%)	47 (1.60%)	0.482	0.018
Golimumab	10 (0.30%)	333 (0.10%)	< 0.001	0.054	10 (0.30%)	10 (0.30%)	1	< 0.001
Vedolizumab	24 (0.80%)	1961 (0.50%)	0.029	0.035	24 (0.80%)	18 (0.60%)	0.353	0.024
Ustekinumab	15 (0.50%)	1907 (0.50%)	0.994	< 0.001	15 (0.50%)	10 (0.30%)	0.316	0.026
Tofacitinib	10 (0.30%)	473 (0.10%)	0.001	0.044	10 (0.30%)	10 (0.30%)	1	< 0.001
Ursodeoxycholate	943 (31.20%)	1775 (0.50%)	< 0.001	0.928	937 (31.20%)	81 (2.70%)	< 0.001	0.821

Abbreviations: diff, difference; IBD, inflammatory bowel disease; N, number; PSC, primary sclerosing cholangitis; PSM, propensity score matching; std, standard.

TABLE 2 | Primary and secondary outcomes.

Outcomes	IBD plus PSC	IBD no PSC	*p*-value	UC plus PSC	UC no PSC	*p*-value	CD plus PSC	CD no PSC	*p*-value
Composite endpoint	54.0%	41.5%	< 0.001	54.3%	42.5%	< 0.001	53.2%	45.6%	< 0.001
Mortality	70.86%	82.62%	< 0.001	17.1%	8.6%	< 0.001	17.2%	7.8%	< 0.01
Hospitalization	66.10%	53.87%	< 0.001	46.8%	37.0%	< 0.001	45.5%	38.9%	= 0.019
Colectomy surgery	12.12%	10.44%	= 0.09	7.8%	6.7%	= 0.383	6.5%	6.6%	= 0.816
Perianal surgery	4.03%	5.44%	= 0.065	NA	NA	NA	1.9%	5.1%	= 0.001

Abbreviations: CD, Crohn's disease; IBD, inflammatory bowel disease; NA, not available; PSC, primary sclerosing cholangitis; UC, ulcerative colitis.

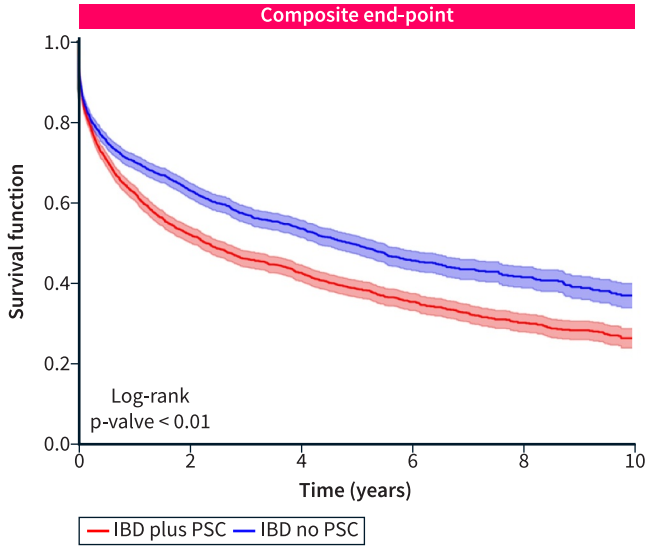

FIGURE 1 | Kaplan–Meier survival analysis showing the risk of experiencing the composite endpoint of surgery, hospitalization and mortality. IBD:IBD patients; PSC-IBD:IBD plus PSC patients.

3.3 | CD Patients

3.3.1 | Primary Endpoint

Filtering data by specific disease, the results were consistent with the overall findings. In the cohort of patients with CD and concomitant PSC, 395 out of 743 patients (53.2%) experienced the composite outcome; in the cohort of patients with CD alone, instead, 339 out of 743 patients (45.6%) experienced the composite outcome. The proportion of CD-plus-PSC patients free from the composite outcome at the end of the observation period was lower (27.36% vs. 30.16%) compared to those with CD alone. Additionally, these patients had an 18.6% higher risk of experiencing the composite outcome (HR 1.18, 95% CI 1.02–1.37) (See Figure 3).

3.3.2 | Secondary Endpoints

Mortality analysis revealed a significant difference between patients with CD who also had PSC and those with CD alone. In the group of 743 patients with both CD and PSC, 128 patients died, resulting in a survival probability of 69.63% at the end of the observation period. In contrast, among the 743 patients with CD alone, only 58 patients died, with a much higher survival probability of 86.49%. The log-rank test yielded a chi-square value of 24.984 ($p < 0.001$) and the hazard ratio was 2.16 (95% CI: 1.58–2.95) (See Figure 4).

Hospitalization rates were notably different between patients with CD and concurrent PSC compared with those with CD alone. In the group with both CD and PSC, 338 out of 743 patients (45.5%) were hospitalized, with a median time to hospitalization of 1.55 days and a survival probability of 35.81% at the end of the observation period. In comparison, among the 743 patients with only CD, 289 patients (38.9%) were hospitalized, with a longer median time to hospitalization of 2339 days and a slightly higher survival probability of 38.91%.The log-rank test indicated a significant difference ($\chi^2 = 5.54$, $p = 0.019$). The hazard ratio was 1.20 (95% CI: 1.03–1.41).

When examining the need for surgery, the outcomes were similar between the two cohorts. In CD-plus-PSC, 48 out of 743 patients (6.5%) required surgery, resulting in a survival probability of 87.92%. Similarly, in CD alone patients, 49 out of 743 patients (6.6%) underwent surgery, with a survival probability of 89.12%.The log-rank test showed no significant difference ($\chi^2 = 0.05$, $p = 0.816$). The hazard ratio was 0.95 (95% CI: 0.64–1.42).

Perianal disease was less common in patients with both CD and PSC compared with those with only CD. In the CD-plus-PSC group, 14 out of 743 patients (1.9%) developed perianal disease, whereas in the CD cohort, 38 out of 743 patients (5.1%) were affected. The survival probability without perianal surgery was 96.71% for the CD plus PSC group and 90.42% for the CD alone group. The log-rank test indicated a significant difference ($\chi^2 = 12.10$, $p = 0.001$). The hazard ratio was 0.35 (95% CI: 0.19–0.65).

4 | UC

4.1 | Primary Endpoint

In the UC plus PSC group, 1224 out of 2254 patients (54.3%) reached the composite outcome, with a median time of 833 days. In the UC group alone, 959 out of 2254 patients (42.5%) reached the composite outcome, with a median time of 1736 days. The proportion of UC-plus-PSC patients free from the

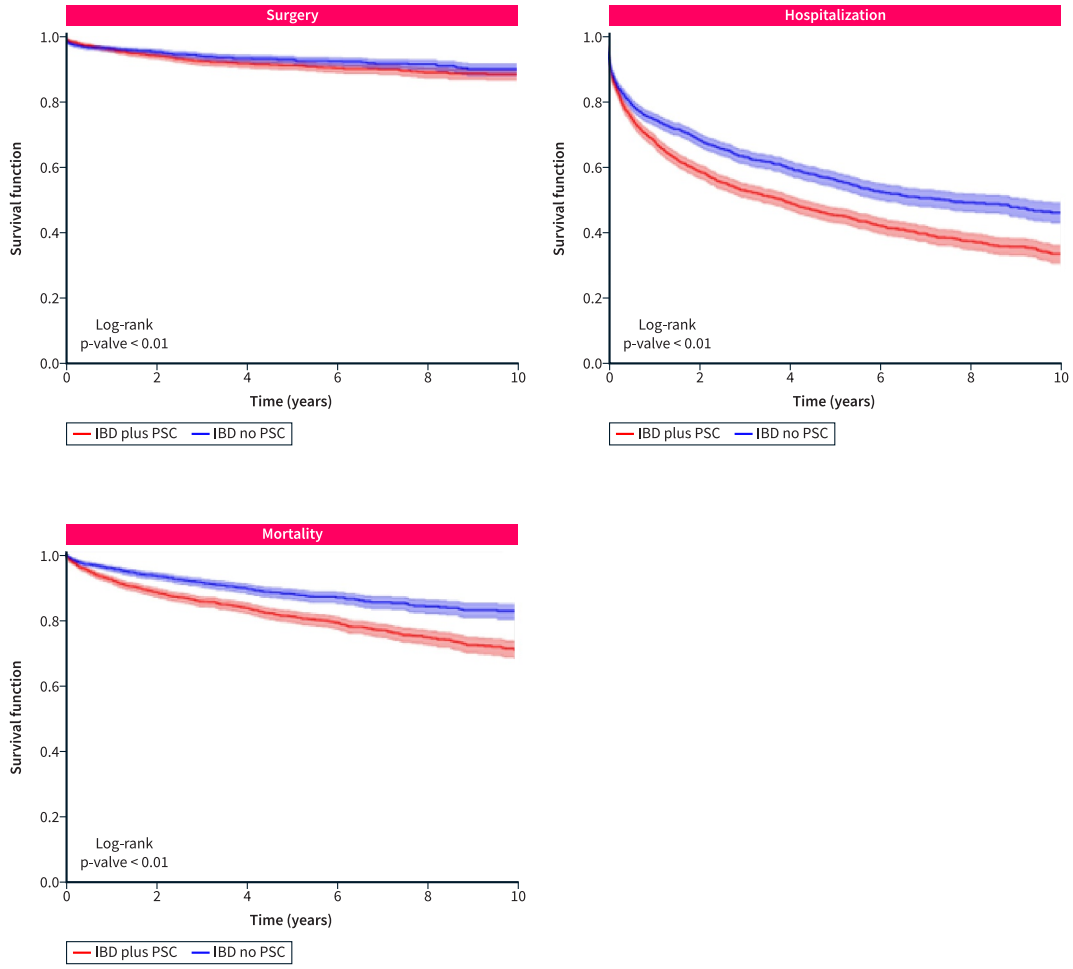

FIGURE 2 | Kaplan–Meier survival analysis showing the risk of experiencing the secondary outcomes of mortality, hospitalization and surgery. IBD: IBD patients; PSC-IBD:IBD plus PSC patients.

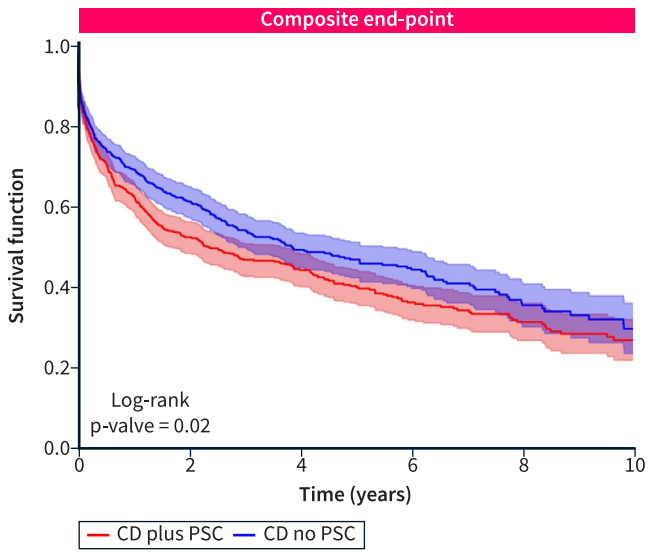

FIGURE 3 | Kaplan–Meier survival analysis showing the risk of experiencing the composite endpoint of surgery, hospitalization and mortality. CD: CD patients; PSC-CD:CD plus PSC patients.

composite outcome at the end of the observation period was lower (26.15% vs. 35.33%) compared with those with UC alone. The log-rank test showed a significant difference ($\chi^2 = 35.94$, $p < 0.001$), with a hazard ratio of 1.29 (95% CI: 1.18–1.40) (See Figure 5).

4.1.1 | Secondary Endpoints

In the UC plus PSC group, 387 out of 2254 patients (17.2%) died, resulting in a survival probability of 71.23% at the end of the observation period. In the UC group alone, 194 out of 2254 patients (8.6%) died, with a survival probability of 83.29%. The log-rank test indicated a significant difference ($\chi^2 = 52.750$, $p < 0.001$), with a hazard ratio of 1.87 (95% CI: 1.57–2.22).

In the UC plus PSC group, 1055 out of 2254 patients (46.8%) were hospitalized, with a median time hospitalize 1338 days. In the UC group alone, 833 out of 2254 patients (37.0%) were hospitalized, with a median time of 2379 days. The probability of being hospitalized by the end of the time window was 66.64%

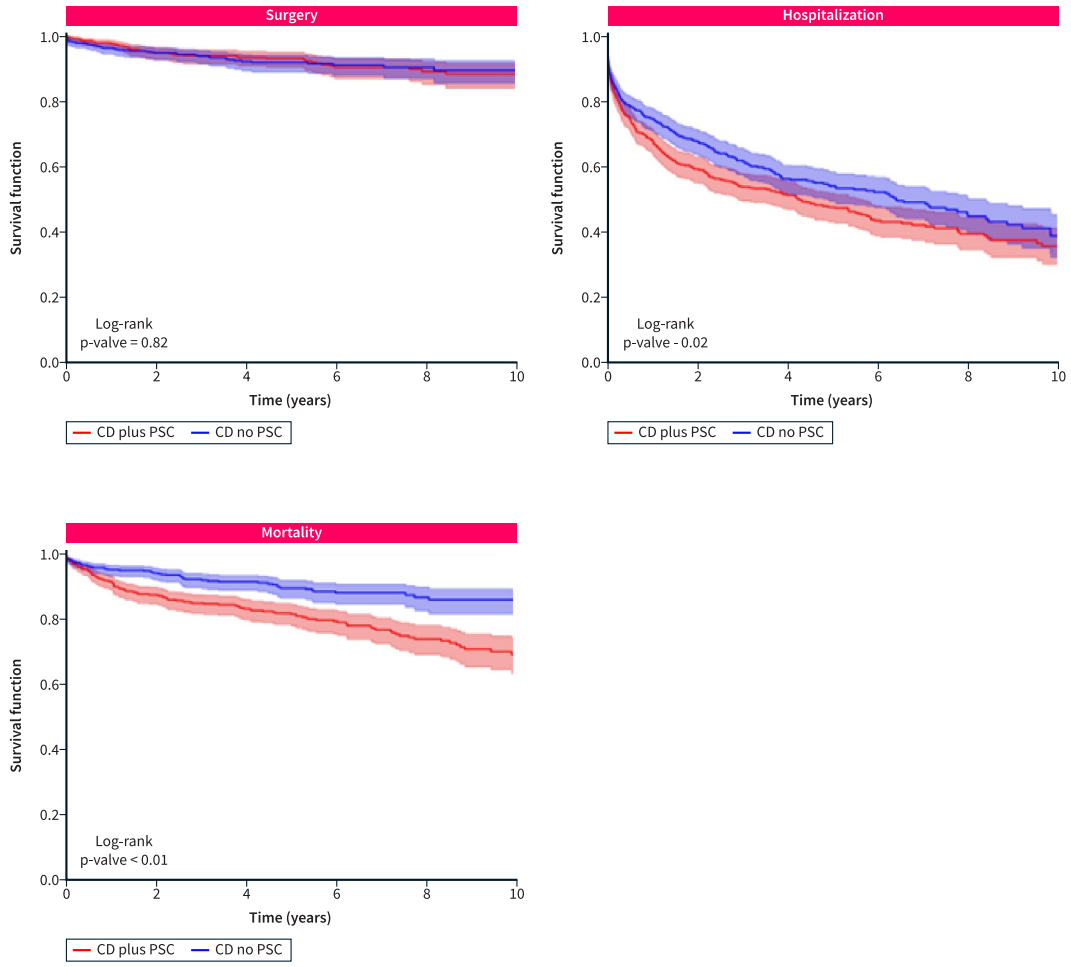

FIGURE 4 | Kaplan–Meier survival analysis showing the risk of experiencing the secondary outcomes of mortality, hospitalization and surgery. CD: CD patients; PSC-CD:CD plus PSC patients.

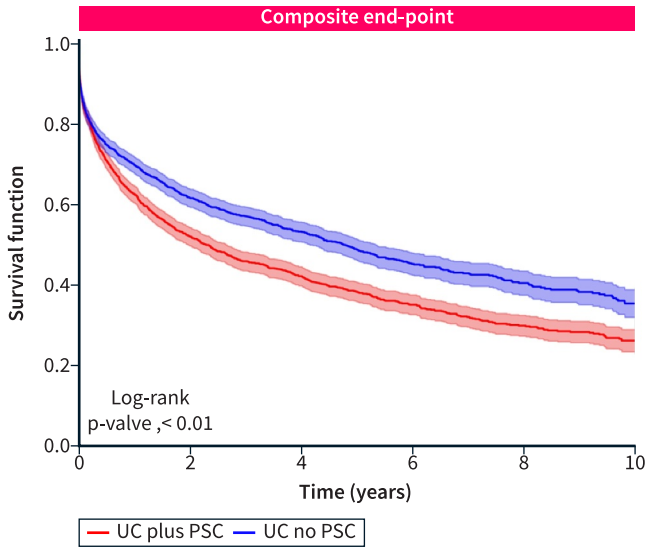

FIGURE 5 | Kaplan–Meier survival analysis showing the risk of experiencing the composite endpoint of surgery, hospitalization and mortality. UC: UC patients; PSC-UC:UC plus PSC patients.

for the UC plus PSC group and 57.11% for the UC alone group. The log-rank test showed a significant difference ($\chi^2 = 28.42$, $p < 0.001$), with a hazard ratio of 1.27 (95% CI: 1.16–1.40).

In total, 175 out of 2254 patients (7.8%) with UC plus PSC underwent surgery, with a survival probability of 87.94%. In the UC group alone, 152 out of 2254 patients (6.7%) underwent surgery, with a survival probability of 89.13%. The log-rank test indicated no significant difference ($\chi^2 = 0.762$, $p = 0.383$), with a hazard ratio of 1.10 (95% CI: 0.88–1.36) (See Figure 6).

5 | Discussion

We conducted a retrospective cohort analysis using the TriNetX database to evaluate the impact of PSC on the prognosis of patients with IBD. Our findings demonstrated that patients with both IBD and PSC had a significantly higher risk of adverse outcomes, including higher mortality, increased hospitalization rates, and a shorter time to the composite endpoint, which included mortality, hospitalization, and colectomy, compared to those with IBD alone. Our results are in line with the literature evidence. Ananthakrishnan and colleagues investigated the association between PSC and cancer risk in a cohort of 11,028 patients with IBD [16]. They identified PSC in 224 patients (2%) and found that those with both IBD and PSC had a significantly higher overall risk of developing cancers compared to IBD patients without PSC, with an odds ratio (OR) of 4.36 (95% CI 2.99–6.37). Specifically, there was a marked increase in the risk of

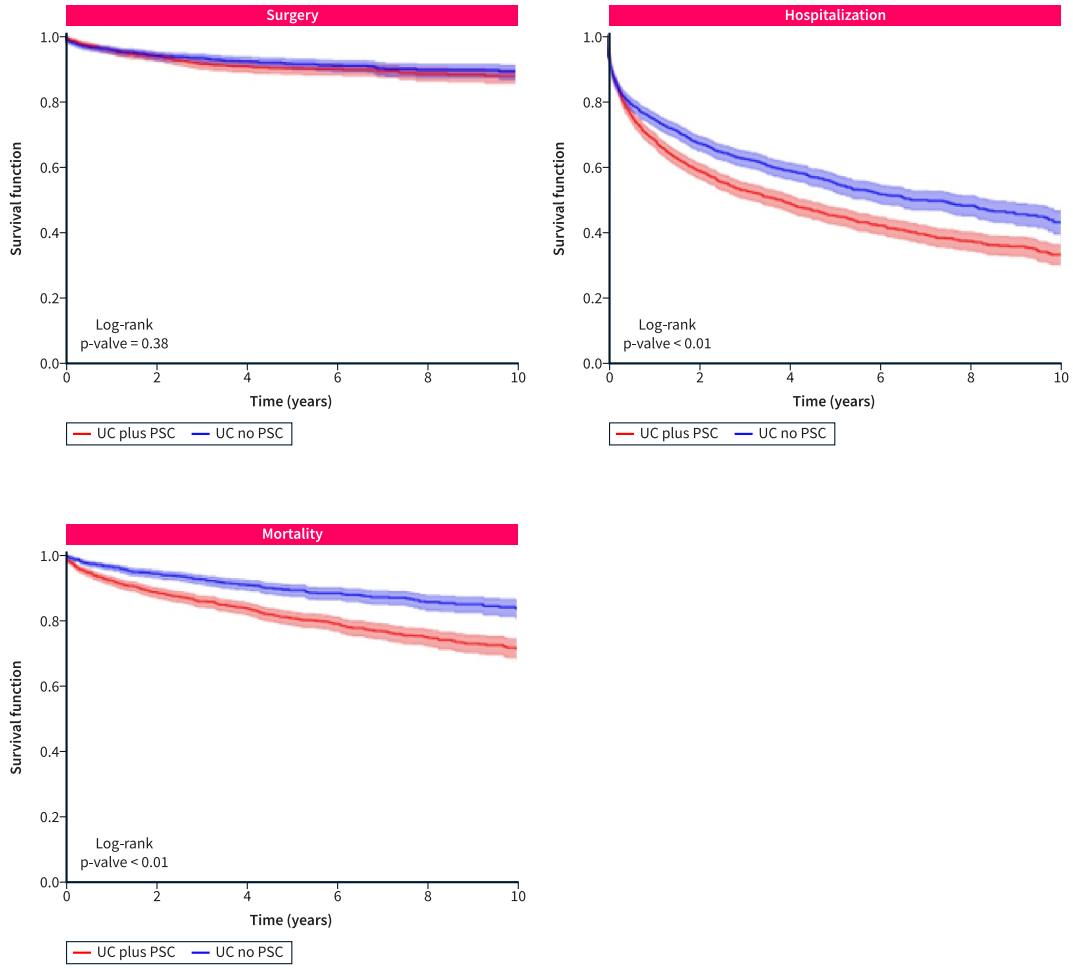

FIGURE 6 | Kaplan–Meier survival analysis showing the risk of experiencing the secondary outcomes of mortality, hospitalization and surgery. UC: UC patients; PSC-UC:UC plus PSC patients.

digestive tract cancers, including digestive tract cancer (OR 10.40, 95% CI 6.86−15.76), pancreatic cancer (OR 11.22, 95% CI 4.11−30.62), colorectal cancer (OR 5.00, 95% CI 2.80−8.95), and cholangiocarcinoma (OR 55.31, 95% CI 22.20−137.80). IBD plus PSC patients also had a higher mortality when compared with IBD patients without PSC (OR 3.51, 95% CI 2.30−5.36) [16]. Similarly, in a 10-year nationwide study by Trivedi et al., patients with PSC and IBD had significantly higher risks of colorectal cancer (HR 2.43, 95% CI), hepatopancreatobiliary cancers (cholangiocarcinoma: HR, 28.46 95% CI; hepatocellular carcinoma: HR, 21.00 95% CI; pancreatic cancer: HR, 5.26 95% CI 2.81−9.84; gallbladder cancer: HR, 9.19 95% CI 2.91−29.05; $P < 0.001$ for all), and mortality (HR 3.20 95% CI 3.01−3.40) compared to those with IBD alone [17]. Conversely, population-level data on the impact of PSC in patients with IBD are lacking. Additionally, few studies explored whether patients with both PSC and IBD have an increased risk of hospitalization or surgery compared with those with IBD alone. A 2018 Danish population-based cohort study revealed that patients with both PSC and IBD have a significantly higher risk of undergoing colectomy compared with IBD patients without PSC. Specifically, the study found that PSC-IBD patients had more than double the risk of requiring resective surgery (HR: 2.13, 95% CI: 1.50−3.03). This increased risk is likely attributed to the more extensive and severe phenotype of IBD observed in PSC-IBD patients, such as the higher prevalence of pancolitis in those with UC and colonic involvement in CD [18]. However, the literature on this topic is not entirely consistent. Other studies suggest that IBD patients with PSC may exhibit a milder IBD phenotype with a less aggressive disease course [19, 20]. For instance, Sano et al. observed that PSC-IBD patients have a right-sided predominance of colonic inflammation, yet none of these patients experienced a severe clinical course, and half were asymptomatic [19]. Another study by Jørgensen et al. highlighted that, while histopathological signs of inflammation in PSC-IBD patients predominantly affected the right colon, the overall inflammatory activity was low, with the majority of patients showing minimal IBD symptoms [20]. Of note, it is well-established that these patients are at a higher risk for non-conventional and non-visible dysplasia, which may be difficult to detect [21]. In cases where high-grade dysplasia is found but cannot be effectively treated endoscopically, or where multifocal low-grade dysplasia is present, colectomy is recommended according to guidelines [22].

Accordingly, we included hospitalization and surgery as key components of our composite outcome and to analyze them as secondary outcomes, with the aim of clarifying these debated

topics. Our study showed that patients with both IBD and PSC had a significantly higher risk of experiencing the composite outcome of mortality, hospitalization, and colectomy compared to patients with IBD alone. Specifically, the survival analysis revealed a 69.7% higher risk of mortality and a 32.6% higher risk of hospitalization for patients with both conditions. However, there were no significant differences in the risk of surgery or perianal disease between the two cohorts, suggesting that PSC does not significantly affect these specific outcomes in IBD patients. When we analyzed the data specifically for UC and CD, the results remained consistent with the overall findings. Patients with CD and concomitant PSC had an 18.6% higher risk of experiencing the composite outcome. In the UC group, the impact of PSC was even more pronounced, with a 29.3% higher likelihood of experiencing the composite outcome (HR 1.293, 95% CI 1.18−1.40). It should be noted, however, that patients with IBD and concomitant PSC undergo annual endoscopic surveillance for colorectal cancer and some of these procedures may have been performed during hospitalization, impacting outcomes [22]. Similar data were previously found in a large international cohort study of 7121 patients with PSC, which demonstrated that patients with UC had a significantly higher risk of disease progression compared to those with CD or without any IBD. Specifically, patients with UC had a 56% increased risk of liver transplantation or death (HR 1.56, $P < 0.001$) and a 45% increased risk of developing hepatopancreatobiliary malignancies than those with CD (HR 1.45, $P < 0.001$) [23]. These results underscore the critical need for tailored management strategies for IBD patients with PSC to improve their prognosis. Indeed, it is worth noting that the importance of surveillance in patients with IBD and PSC is already underlined in major international guidelines: an annual colonoscopy should be performed from the diagnosis of PSC due to the increased risk of colorectal cancer and an appropriate surveillance with adequate imaging (preferably with MRI/MRCP with or without serum CA 19-9) for cholangiocarcinoma risk every 12 months [22, 24–26].

The pathophysiological link underlying the worse prognosis observed in patients with both PSC and IBD remains unclear. Nevertheless, this observation suggests that these patients may be challenging to treat, although a recent international consensus meeting rejected extraintestinal manifestations such as PSC as defining criteria for difficult-to-treat IBD, as they might coexist with IBD without necessarily affecting its management [27]. Our data, on the other hand, highlight the poorer prognosis associated with a concomitant diagnosis of PSC, suggesting that it may be rational to consider a top-down approach for these patients, intensifying therapy to mitigate the risk of negative outcomes [28, 29]. Evidence of currently available therapies in the management of patients with IBD and concomitant PSC shows how the effect on intestinal disease is generally reduced compared to patients who do not have PSC [30]. On the other hand, the drugs currently available have a non-significant effect on liver biochemistry [30, 31]. Additionally, further studies are warranted to evaluate whether effective treatment and control of PSC might influence the management of IBD and potentially lead to improved patient outcomes.

To the best of our knowledge, this is the largest cohort to assess the prognosis of patients with IBD and concomitant PSC. Moreover, there are other strengths of our study including the extended follow-up period, which spans up to 20 years, allowing for a comprehensive evaluation of long-term outcomes. Additionally, we employed robust statistical methods, including propensity score matching, to ensure a balanced comparison between the IBD with PSC cohort and the IBD without PSC cohort. However, there are some limitations to address. The retrospective nature of our study and the extended study period introduce biases, preventing the establishment of causality between PSC and observed outcomes in IBD patients. The database does not allow the detection of specific causes of mortality, surgery, and hospitalization preventing the association with IBD and PSC from being defined. Despite the effort to include all important variables in the propensity matching, residual confounding is still possible. Indeed, the differences in the use of specific medications (especially immunosuppressants) could confound the outcomes and the use of propensity score matching might not fully account for unmeasured confounders or the potential impact of selection bias on the observed outcomes. Furthermore, our study was limited by the lack of clinical details (such as disease severity, disease duration, Montreal classification, PSC staging, family history, medication adherence, and undiagnosed PSC in IBD patients) and endoscopic data, which could provide deeper insights into disease progression and severity. Additionally, the relatively small number of patients on biological therapies (1%–2%) and on ursodeoxycholic acid (~33%) limits our ability to assess their impact on the prognosis. The reason for the low use of advanced therapies for IBD and ursodeoxycholic acid in our population is not known, but the broad enrollment window of the study (since 2003) could have influenced the underuse and the negative outcomes [32, 33]. It is worth noting that the effects of biological therapies on PSC remain uncertain [34]. These drugs could potentially influence PSC either through direct effects on the liver or by improving the control of immunological mechanisms in the colon [34]. A recent meta-analysis suggested that biological drugs for IBD do not lead to an improvement of biochemical markers of cholestasis in patients with PSC [35]. Understanding whether advanced therapies directly impact PSC progression or through better management of intestinal disease is crucial. This knowledge gap highlights the need for further research to explore the impact of advanced therapies on PSC and their potential role in reducing the risk of related malignancies. Overall, while no pharmacological treatment has proven effective for PSC to date, ongoing research continues to explore new therapeutic approaches that could improve patient outcomes and clarify the complex interplay between IBD, PSC, and advanced treatments.

In conclusion, this study demonstrates that the presence of IBD and concomitant PSC is associated with worse outcomes compared to those with IBD alone, with higher mortality and hospitalization rates. Further research is needed to understand the impact of advanced therapies on PSC and to refine management and follow-up strategies for these patients.

Author Contributions

M.A., F.D., and S.D. conceived the study. F.L. and F.D. wrote the manuscript and created tables and figures. All authors approved and contributed to the final manuscript.

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Conflicts of Interest

Ferdinando D'Amico has served as a speaker for Abbvie, Sandoz, Janssen, Galapagos, Takeda, Tillotts, and Omega Pharma; he has also served as advisory board member for Abbvie, Ferring, Galapagos, Janssen, Takeda, and Nestlè. Mariangela Allocca received consulting fees from Nikkiso Europe, Mundipharma, Janssen, Abbvie and Pfizer. Francesca Lusetti declares no conflict of interest. Tommaso Lorenzo Parigi declares no conflict of interest. Francesca Rusconi and Gema Hernandez are employees of TriNetX Europe NV. Alba Segovia-Hilara declares no conflict of interest. Virginia Solitano declares no conflict of interest. Alessandra Zilli received lecture fees from Pfizer, Abbvie, Takeda, Sandoz, Galapagos, Janssen and consulting fees from Pfizer, Abbvie, Takeda, Cadigroup, Tillotts Pharma, Janssen. Federica Furfaro received consulting fees from Amgen, Galapagos, Tillots, Lilly and Abbvie and lecture fees from Lilly, Janssen, Abbvie and Pfizer. Gionata Fiorino received consultancy fees from Ferring, MSD, AbbVie, Takeda, Janssen, Amgen, Sandoz, Samsung Bioepis, Celltrion. Vipul Jairath has received consultancy/advisory board fees from AbbVie, Alimentiv, Arena Pharmaceuticals, Asahi Kasei Pharma, Asieris, AstraZeneca, Bristol Myers Squibb, Celltrion, Eli Lilly, Ferring, Flagship Pioneering, Fresenius Kabi, Galapagos, GlaxoSmithKline, Genentech, Gilead, Janssen, Merck, Mylan, Pandion, Pendopharm, Pfizer, Protagonist, Reistone Biopharma, Roche, Sandoz, Second Genome, Takeda, Teva, Topivert, Ventyx, and Vividion, and speaker's fees from AbbVie, Ferring, Galapagos, Janssen Pfizer Shire, Takeda, and Fresenius Kabi. Pietro Invernizzi declares no conflict of interest. Laurent Peyrin-Biroulet has served as a speaker, consultant and advisory board member for Merck, Abbvie, Janssen, Genentech, Mitsubishi, Ferring, Norgine, Tillots, Vifor, Hospira/Pfizer, Celltrion, Takeda, Biogaran, Boerhinger-Ingelheim, Lilly, HAC Pharma, Index Pharmaceuticals, Amgen, Sandoz, Forward Pharma GmbH, Celgene, Biogen, Lycera, Samsung Bioepis, Theravance. Silvio Danese has served as a speaker, consultant, and advisory board member for Schering-Plough, AbbVie, Actelion, Alphawasserman, AstraZeneca, Cellerix, Cosmo Phar-maceuticals, Ferring, Genentech, Grunenthal, Johnson and Johnson, Millenium Takeda, MSD, Nikkiso Europe GmbH, Novo Nordisk, Nycomed, Pfizer, Pharmacosmos, UCB Pharma and Vifor.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.