**Supplementary Data Legend:**

Supplementary Table 1:Treatments exposure at or after diagnosis.

Supplementary Table 2**:**  Laboratory data at diagnosis and during patient’s follow-up before first clinical relapse.

Supplementary Table 3: Clinical relapse according to patients clinical, endoscopic, histological and laboratory characteristics and their treatments exposure (bivariate analyses).

Supplementary Table 4: Sensitivity analyses in model 1: factors associated with clinical relapses: first multivariable Cox regression model including clinical, endoscopic, histological and therapeutic variables without median CRP level.

Supplementary Figure 1: Flowchart of the cohort.

Supplementary Figure 2: Kaplan-Meier curve representing patients time to relapse according to oral corticosteroids exposure at induction.

Supplementary Figure 3: Kaplan-Meier curve representing patients time to relapse according to TNF-alpha inhibitor exposure at induction.

Supplementary Figure 4: Kaplan-Meier curve representing time to relapse according to the sex in patients 13 years old and older.

Supplementary Figure 5: Kaplan-Meier curve representing patients time to relapse according to presence of increased tissue eosinophils.

***Supplementary data:***

Table 1.Treatments exposure at or after diagnosis

|  |  |
| --- | --- |
| **Total, Nb.**  | 639 |
| **First induction treatment administered, Nb. (%)a** |  |
| EENb | 136 (21.6) |
| Corticosteroids (IVc, oral) | 315 (49.9) |
| Oral 5-ASAd | 114 (18.1) |
| TNF-alpha inhibitors | 66 (10.5) |
| **IV corticosteroids exposure at inductione, Nb. (%)** | 149 (23.6) |
| Time to initiation of IV corticosteroids as induction therapy f, median (IQRg), days | 0.0 (0.0-2.0) |
| **Oral corticosteroids exposure at induction, Nb. (%)** | 391 (61.2) |
| Time to initiation of oral corticosteroids as induction therapy, median (IQR), days | 3.0 (0.0-14.0) |
| **EEN exposure at induction, Nb. (%)** | 188 (29.8) |
| Time to initiation of EEN as induction therapy, median (IQR), days | 3.0 (1.0-7.0) |
| **Oral 5-ASA exposure at induction, Nb. (%)** | 150 (23.8) |
| Time to initiation of oral 5-ASA as induction therapy, median (IQR), days | 7.5 (0.0-34.0) |
| **TNF-alpha inhibitors exposure at induction, Nb. (%)** | 247 (37.9) |
| Time before the initiation of TNF-alpha inhibitors as induction therapy, median (IQR), days | 24.0 (5.0-73.0) |
| **Antibiotic exposure at diagnosis, Nb. (%)** | 118 (18.5) |
| **First maintenance treatment administered, Nb. (%)** |  |
| Thiopurines | 164 (26.3) |
| Methotrexate | 96 (15.4) |
| TNF-alpha inhibitors | 261 (41.8) |
| Oral 5-ASA | 103 (16.5) |
| **Treatments exposure before the first relapse** |  |
| TNF-alpha inhibitor exposure, Nb. (%) | 368 (57.6) |
| Time to initiation of TNF-alpha inhibitors, median (IQR), days | 59.5 (12.5-161.0) |
| Methotrexate exposure, Nb. (%) | 168 (26.3) |
| Time to initiation of Methotrexate, median (IQR), days | 64.5 (26.0-214.5) |
| Thiopurines exposure, Nb. (%) | 225 (35.2) |
| Time to initiation of thiopurines, median (IQR), days | 35.0 (18.0-92.0) |
| Oral 5-ASA exposure, Nb. (%) | 174 (27.2) |
| Time to initiation of oral 5-ASA, median (IQR), days | 25.0 (1.0-80.0) |
| **Surgery before relapse, Nb. (%)** | 43 (6.7) |

a All percentages are column proportions. b EEN: Exclusive enteral nutrition. c IV: Intravenous.  d 5-Aminosalicylates.**e** Including taking the treatment in monotherapy or in combo-therapy before initial remission. **f** All treatments initiation times are calculated from the date of diagnosis. g IQR: Interquartile range.  h Antibiotic exposure within +/- 15 days of diagnosis.

***Supplementary data:***
Table 2**.**  Laboratory data at diagnosis and during patient’s follow-up before first clinical relapsea

|  |  |  |
| --- | --- | --- |
|  |  | Normal range |
| **Laboratory data at diagnosis** |  |  |
| Hemoglobin, median (IQRb), g/L (n=612) | 117.0 (107.0-127.0) | 135.0-175.0 c |
| Albumin, median (IQR), g/L (n=596) | 32.3 (28.0-37.0) | 38.0-50.0 |
| C-reactive protein, median (IQR), mg/L (n=587) | 25.6 (6.7-57.5) | 0-1.7 |
| Erythrocyte sedimentation rate, median (IQR), mm/h (n=537) | 32.0 (20.0-44.0) | 0-13.0 |
| Fecal calprotectin, median (IQR), ug/g (n=181) | 1233.0 (510.0-2100.0) | < 150 |
| **Laboratory data during patient’s follow-up** |  |  |
| Hemoglobin, median (IQR), g/L (n=639) | 122.5 (114.0-131.0) | 135.0-175.0 b |
| Albumin, median (IQR), g/L (n=639) | 37.5 (34.0-40.5) | 38.0-50.0 |
| C-reactive protein, median (IQR), mg/L (n=636) | 5.1 (1.7-15.8) | 0-1.7 |
| Erythrocyte sedimentation rate, median (IQR), mm/h (n=616) | 20.0 (12.0-29.0) | 0-13.0 |
| Fecal calprotectin, median (IQR), ug/g (n=364) | 307.5 (117.5-1000.0) | < 150 |
| **Treatments’ laboratory data** |  |  |
| Infliximab levels, median (IQR), ug/mL (n=228) | 6.7 (4.4 – 10.4) | 3.0-7.0 |
| Median infliximab level < 7 ug/mL, Nb. (%)  | 120 (52.6) | - |
| Anti-infliximab antibody, median (IQR), U/mL (n=182) | 7.0 (3.0-29.0) | 0 |
| 6-TGN leveld, median (IQR), pmol/8\*10^8 érythrocytes (n=169) | 177.5 (136.0-231.0) | ≥ 250 |
| 6-TGN level < 250 pmol/8\*10^8 erythrocytes, Nb. (%) | 137 (81.07) | - |

a Median values during patient’s follow-up before first clinical relapse. b IQR: Interquartile range. c Depends on patient’s gender and age. d 6-TGN: 6-thioguanine nucleotide level.

***Supplementary data:***
Table 3. Clinical relapse according to patients clinical, endoscopic, histological and laboratory characteristics and their treatments exposure (bivariate analyses).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Patients who have not relapsed | Patients who haverelapsed | Bivariate HR [95% CIa] | *p* Value |
| **Total, Nb. (%)b** | 257 (40.2) | 382 (59.8) |  |  |
| **CLINICAL DATE** |  |  |  |  |
| **Age, median (IQR), years** | 14.7 (12.2-16.2) | 13.5 (11.1-15.2) | 0.98 [0.95; 1.02] | 0.28 |
| **Sex, Nb. (%)** |  |  |  |  |
| Male | 162 (63.0) | 194 (50.8) | 1 | 0.0006 |
| Female | 95 (37.0) | 188 (49.2) | 1.43 [1.16; 1.74] |
| **Weight z-score, median (IQR)** | -0.6 (-1.5-0.3) | -0.6 (-1.4-0.2) | 1.00 [0.93; 1.08] | 0.91 |
| **Height z-score, median (IQR)** | -0.2 (-0.9-0.5) | -0.2 (-0.9-0.4) | 0.99 [0.90; 1.08] | 0.75 |
| **BMIc z-score, median (IQR)** | -0.9 (-1.7-0.4) | -0.7 (-1.6-0.1) | 1.02 [0.95; 1.10] | 0.52 |
| **PCDAId, median (IQR)** | 32.5 (25.0-40.0) | 35.0 (27.5-47.5) | 1.01 [1.01; 1.02] | 0.01 |
| **Symptoms at diagnosis, Nb. (%)** |  |  |  |  |
| Abdominal pain | 227 (88.3) | 348 (91.1) | 1.25 [0.88; 1.78] | 0.21 |
| Asthenia | 106 (41.3) | 185 (48.4) | 1.16 [0.95; 1.41] | 0.16 |
| Fever | 43 (16.7) | 87 (22.8) | 1.18 [0.93; 1.50] | 0.17 |
| Diarrhea | 163 (63.4) | 283 (74.1) | 1.40 [1.11; 1.76] | 0.004 |
| Rectal bleeding | 96 (37.4) | 190 (49.7) | 1.43 [1.17; 1.75] | 0.0005 |
| Vomiting | 52 (20.2) | 73 (19.1) | 1.01 [0.78; 1.30] | 0.96 |
| Weightloss | 154 (59.9) | 249 (65.2) | 1.05 [0.85; 1.29] | 0.68 |
| **Paris Classificatione** |  |  |  |  |
| **Age at diagnosis, Nb. (%)** |  |  |  |  |
| A1a | 23 (9.0) | 54 (14.1) | 1 | 0.19 |
| A1b | 216 (84.1) | 307 (80.4) | 0.80 [0.60; 1.07] |
| A2 | 18 (7.0) | 21 (5.5) | 1.17 [0.71; 1.95] |
| **Location of digestive involvement, Nb. (%)** |  |  |  |  |
| L1 | 92 (35.8) | 87 (22.8) | 1 | 0.004 |
| L2 | 43 (16.7) | 102 (26.7) | 1.63 [1.22; 2.16] |
| L3 | 116 (45.1) | 190 (49.7) | 1.34 [1.04; 1.72] |
| L4a isolated | 1 (0.4) | 0 (0.0) | - |
| L4b isolated | 2 (0.8) | 1 (0.3) | - |
| L4ab isolated | 3 (1.2) | 2 (0.5) | - |
| **Upper digestive tract involvement, Nb. (%)** |  |  |  |  |
| None | 91 (35.4) | 131 (34.3) | 1 | 0.36 |
| L4a | 107 (41.6) | 175 (45.8) | 1.08 [0.86; 1.35] |
| L4b | 23 (9.0) | 23 (6.0) | 0.74 [0.47; 1.15] |
| L4ab | 36 (14.0) | 53 (13.9) | 1.00 [0.73; 1.38] |
| **Disease phenotype, Nb. (%)** |  |  |  |  |
| B1 | 211 (82.4) | 330 (86.4) | 1 | 0.59 |
| B2 | 23 (9.0) | 29 (7.6) | 0.92 [0.63; 1.34] |
| B3 | 14 (5.5) | 18 (4.7) | 1.01 [0.63; 1.63] |
| B2B3 | 8 (3.1) | 5 (1.3) | 0.55 [0.23; 1.34] |
| **Presence of inflammatory perianal involvementf, Nb. (%)** | 97 (37.7) | 102 (26.7) | 0.77 [0.61; 0.97] | 0.02 |
| **Presence of perianal abscesses/fistulas, Nb. (%)** | 66 (25.7) | 54 (14.1) | 0.65 [0.49; 0.87] | 0.004 |
| **Extra-intestinal manifestations, Nb. (%)** |  |  |  |  |
| Aphtous stomatitis | 51 (19.8) | 101 (26.4) | 1.21 [0.96; 1.51] | 0.11 |
| Arthralgia | 46 (17.9) | 72 (18.9) | 1.05 [0.82; 1.36] | 0.69 |
| Arthritis | 16 (6.2) | 21 (5.5) | 0.89 [0.58; 1.39] | 0.61 |
| Erythema nodosum | 11 (4.3) | 10 (2.6) | 0.79 [0.42; 1.49] | 0.47 |
| Skin rash | 17 (6.6) | 19 (5.0) | 0.86 [0.54; 1.36] | 0.52 |
| **Time to first remission (days)** | 109.0 (53.0-186.0) | 66.0 (39.0-140.0) | 0.99 [0.99; 1.00] | 0.001 |
| **First remission achieved before 12 weeks after diagnosis, Nb. (%)** | 102 (39.7) | 232 (60.7) | 1.66 [1.35; 2.04] | < 0.0001 |
| **ENDOSCOPIC AND HISTOLOGIC DATAg** |  |  |  |  |
| **SES-CDh, median (IQR)** | 9.0 (6.0-15.0) | 12.0 (9.0-20.0) | 1.02 [1.01; 1.03] | 0.002 |
| **Presence of architectural distortions, Nb. (%)** | 174 (71.0) | 185 (71.4) | 1.55 [1.19; 2.03] | 0.001 |
| **Presence of moderate to severe lymphoplasmacyticl infiltrate, Nb. (%)** | 198 (80.8) | 314 (85.3) | 1.25 [0.94; 1.67] | 0.13 |
| **Signs of moderate to severe active inflammation, Nb. (%)** | 142 (58.0) | 246 (66.9) | 1.33 [1.07; 1.65] | 0.01 |
| **Presence of granulomas, Nb. (%)** | 91 (37.1) | 162 (44.0) | 1.20 [0.98; 1.48] | 0.08 |
| **Increased eosinophils, Nb. (%)** | 117 (47.8) | 234 (63.6) | 1.41 [1.14; 1.75] | 0.002 |
| **Presence of lymphoïd follicles, Nb (%)** | 144 (58.8) | 223 (60.6) | 1.02 [0.83; 1.26] | 0.82 |
| **TREATMENTS DATA** |  |  |  |  |
| **First induction treatment administered, Nb. (%)** |  |  |  |  |
| TNF-alpha inhibitors | 39 (15.7) | 27 (7.1) | 1 | 0.01 |
| Corticosteroids (IVi, oral) | 110 (44.2) | 205 (53.7) | 1.93 [1.29; 2.89] |
| Oral 5-ASAj | 40 (16.1) | 74 (19.4) | 1.74 [1.12; 2.70] |
| EENk | 60 (24.1) | 76 (19.9) | 1.57 [1.01; 2.44] |
| **IV corticosteroids exposure at induction, Nb. (%)** | 48 (19.3) | 101 (26.4) | 1.20 [0.95; 1.50] | 0.12 |
| **Oral corticosteroids exposure at induction, Nb. (%)** | 139 (54.1) | 252 (66.0) | 1.26 [1.02; 1.55] | 0.03 |
| **Oral 5-ASA exposure at induction, Nb. (%)** | 53 (21.3) | 97 (25.4) | 1.07 [0.85; 1.35] | 0.57 |
| **EEN exposure at induction, Nb. (%)** | 81 (32.5) | 107 (28.0) | 0.88 [0.70; 1.10] | 0.25 |
| **TNF-alpha inhibitors exposure at induction, Nb. (%)** | 125 (48.6) | 117 (30.6) | 0.64 [0.51; 0.79] | < 0.0001 |
| **Antibiotics exposure at diagnosisL, Nb. (%)** | 53 (20.6) | 65 (17.0) | 0.82 [0.63; 1.07] | 0.14 |
| **First maintenance treatment administered, Nb. (%)** |  |  |  |  |
| TNF-alpha inhibitors | 137 (55.7) | 125 (33.1) | 1 | < 0.0001 |
| Methotrexate | 33 (13.4) | 62 (16.4) | 1.59 [1.17; 2.16] |
| Thiopurines | 43 (17.5) | 121 (32.0) | 1.84 [1.43; 2.36] |
| Oral 5-ASA | 33 (13.4) | 70 (18.5) | 1.64 [1.22; 2.20] |
| **TNF-alpha inhibitors exposure before first remissionm, Nb. (%)** | 127 (80.9) | 112 (53.1) | 0.42 [0.32; 0.55] | < 0.0001 |
| **TNF-inhibitors exposure within one month of diagnosism, Nb. (%)** | 60 (38.2) | 73 (34.6) | 0.84 [0.63; 1.12] | 0.23 |
| **Methotrexate exposure before first remissionn, Nb. (%)** | 41 (74.6) | 60 (53.1) | 0.55 [0.38; 0.79] | 0.0001 |
| **Methotrexate exposure within one month of diagnosisn, Nb. (%)** | 19 (34.6) | 28 (24.8) | 0.82 [0.53; 1.26] | 0.34 |
| **Thiopurines exposure before first remissiono, Nb. (%)** | 47 (79.7) | 116 (69.9) | 0.72 [0.51; 1.00] | 0.05 |
| **Thiopurines exposure within one month of diagnosiso, Nb. (%)** | 46 (78.0) | 118 (71.1) | 0.83 [0.59; 1.17] | 0.28 |
| **Oral 5-ASA exposure before first remissionp, Nb. (%)** | 47 (94.0) | 94 (75.8) | 0.36 [0.24; 0.55] | <0.0001 |
| **Oral 5-ASA exposure within one month of diagnosisp, Nb. (%)** | 40 (80.0) | 92 (74.2) | 0.73 [0.49; 1.10] | 0.13 |
| **LABORATORY DATA** |  |  |  |  |
| **Laboratory data at diagnosisq** |  |  |  |  |
| Hemoglobin at diagnosis, median (IQR), g/L | 118.0 (108.0-128.0) | 116.0 (107.0-126.0) | 1.00 [0.99; 1.01] | 0.69 |
| Albumin at diagnosis, median (IQR), g/L | 33.0 (29.0-37.0) | 32.0 (28.0-37.0) | 1.00 [0.98; 1.02] | 0.98 |
| C-reactive protein at diagnosis, median (IQR), mg/L | 22.9 (5.2-60.8) | 30.0 (8.3-56.6) | 1.00 [1.00; 1.00] | 0.58 |
| Erythrocyte sedimentation rate at diagnosis, median (IQR), mm/h | 29.0 (19.0-42.0) | 34.0 (22.0-45.0) | 1.01 [1.00; 1.02] | 0.06 |
| Fecal calprotectin at diagnosisL, median (IQR), ug/g | 1512.0 (566.0-2100.0) | 1034.0 (399.0-1800.0) | 0.98 [0.96; 1.01] | 0.98 |
| **Laboratory data between diagnosis and initial relapse** |  |  |  |  |
| Median hemoglobin level, median (IQR), g/L | 127.0 (119.0-135.0) | 119.5 (112.0-127.0) | 0.97 [0.96; 0.98] | < 0.0001 |
| Median albumin level, median (IQR), g/L | 39.0 (35.9-42.0) | 36.5 (32.0-39.5) | 0.90 [0.89; 0.92] | < 0.0001 |
| Median C-reactive protein level, median(IQR), mg/L | 3.9 (1.2-8.9) | 8.1 (2.5-21.7) | 1.01 [1.01; 1.02] | < 0.0001 |
| Median erythrocyte sedimentation rate level, median (IQR), mm/h | 15.0 (8.0-25.0) | 22.3 (16.0-32.0) | 1.03 [1.03; 1.04] | < 0.0001 |
| Median fecal calprotectin levelr, median(IQR), ug/g | 209.0 (84.0- 571.0) | 621.5 (282.0-1344.0) | 1.08 [1.06; 1.10] | < 0.0001 |
| **Laboratory data on treatments between diagnosis and initial relapse** |  |  |  |  |
| Median 6-TGN level, median (IQR), pmol/8\*108 erythrocytes | 173.0 (137.0-215.5) | 176.0 (130.0-231.0) | 1.00 [1.00; 1.00] | 0.51 |
| Median 6-TGN level < 250 pmol/8\*108 érythrocytes, Nb. (%) | 48 (87.3) | 89 (78.1) | 0.78 [0.50; 1.22] | 0.28 |
| Median infliximab levels, median (IQR), ug/mL | 6.7 (4.2-9.3) | 5.9 (3.0-10.6) | 1.03 [0.99; 1.06] | 0.11 |
| Median infliximab level ≥ 7 ug/mL, Nb. (%) | 63 (48.5) | 37 (37.0) | 0.81 [0.54; 1.22] | 0.31 |
| Proportion of infliximab dosages at a level ≥ 7 ug/Ml, % | 50.0 (20.0-75.0) | 33.3 (0.0-69.0) | 1.00 [0.99; 1.00] | 0.08 |
| Less than 50% of infliximab dosages at a level ≥ 7 ug/Ml, Nb (%) | 191 (74.3) | 340 (89.0) | 1.98 [1.44; 2.73] | < 0.0001 |
| Median anti-infliximab antibody levels, U/L | 7.5 (4.0-29.0) | 5.00 (2.0-28.0) | 1.00 [1.00; 1.00] | 0.81 |

a 95% CI: 95% confidence interval.  b All percentages are colum proportions. c BMI: Body Mass Index. d PCDAI: Pediatric Crohn’s Disease Activity Index. e Crohn’s disease localized to the distal one-third of the ileum ± limited caecal involvement is defined as L1, isolated colitis as L2, and ileocolonic disease as L3. Upper gastrointestinal tract involvement is designated L4a when proximal to the ligament of Treitz and L4b if distal to the ligament of Treitz but proximal to the distal one-third of the ileum. Disease behavior is classified as: inflammatory (B1), structuring (B2), penetrating (B3); or structuring and penetrating (B2B3). A1a CD includes patients aged less than 10 years-old, A1b CD includes patients aged between 10 and 17 years old and A2 CD includes patients aged more than 17 years old. f Inflammatory perianal involvement includes inflammatory fissures in addition to perianal fistulas and abcesses. g Findings on histology including those on OGD and colonoscopy.  h SES-CD: Simple Endoscopic Score for Crohn’s Disease, including only patients who had a complete successful colonoscopy at diagnosis (visualization of the rectum to the ileum), n=503. i IV: intravenous. j 5-aminosalicylates. k EEN: Exclusive enteral nutrition. L Antibiotics exposure within +/- 15 days of diagnosis.
m These analyzes were only done in patients who started their TNF-alpha inhibitors treatment before initial relapse. n These analyzes were only done in patients who started their methotrexate treatment before initial relapse. o These analyzes were only done in patients who started their thiopurines treatment before initial relapse. p These analyzes were only done in patients who started their oral 5-ASA treatment before initial relapse. q Measure of the laboratory parameter closest to the date of diagnosis within +/- 1 month.  r HR of each increase of 100 ug/g of FC.

***Supplementary data:***

Table 4. Sensitivity analyses in model 1: factors associated with clinical relapses: first multivariable Cox regression model including clinical, endoscopic, histological and therapeutic variables without median CRP levela

|  |  |  |
| --- | --- | --- |
|  | aHR [95% CI] | *p* Value |
| **Female sex** | 1.48 [1.16; 1.88] | 0.001 |
| **Location of digestive involvementb, Nb. (%)** |  |  |
| L1 | 1 |  |
| L2 | 1.52 [1.07; 2.14] | 0.02 |
| L3 | 1.16 [0.86; 1.56] | 0.32 |
| **First maintenance treatment** |  |  |
| TNF-alpha inhibitors | 1 |  |
| Oral 5-ASAc | 1.71 [1.19; 2.46] | 0.004 |
| Methotrexate | 1.77 [1.23; 2.53] | 0.002 |
| Thiopurines | 1.73 [1.28; 2.33] | 0.0004 |
| **Presence of granulomas on biopsies at diagnosis** | 1.43 [1.12; 1.81] | 0.004 |
| **Increased eosinophils on biopsies at diagnosis** | 1.30 [1.01; 1.67] | 0.04 |
| **First remission achieved before**$ $**12 weeks after diagnosis** | 1.75 [1.37; 2.25] | <0.0001 |

a Results from a multivariable Cox regression model including only the variables that were significantly associated with relapse in bivariate analyzes. Model adjusted on year of diagnosis, PCDAI at diagnosis, SES-CD at diagnosis (for patients with complete colonoscopy) and presence of perianal involvement during follow-up and induction treatments. All the variables not displayed in this table were statistically unsignificant in the multivariable Cox model. The sample size decreased from 639 to 446 due to the fact that some variables included in the model were not available for all patients in the cohort and could not be imputed. b Crohn’s disease localized to the distal one-third of the ileum ± limited caecal involvement is defined as L1, isolated colitis as L2, and ileocolonic disease as L3. c 5-Aminosalicylates.