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Original Article

Lymphoma in Patients with Inflammatory Bowel Disease: A Multicentre Collaborative Study Between GETAID and LYSA

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Abstract

Background: Inflammatory bowel disease [IBD] is associated with an increased risk of developing lymphoma. Although recent data have clarified the epidemiology of lymphoma in IBD patients, the clinical and pathological characteristics of lymphoma in IBD remain poorly known.

Methods: Patients with IBD and lymphoma were retrospectively identified in the framework of a national collaborative study including the Groupe d'Étude Thérapeutique des Affections Inflammatoires du Tube Digestif [GETAID] and the Lymphoma Study Association [LYSA]. We characterized clinical and prognostic features for the three most frequent lymphoma subtypes occurring in IBD. We performed a multicentre case-control study. Controls [lymphoma *de novo*] were matched [5:1] to cases on gender, age at diagnosis, lymphoma subtype, year of diagnosis, and IPI/FLIPI indexes. Overall survival and progression-free survival were compared between cases and controls.

Results: In total, 133 IBD patients with lymphoma were included [males = 62.4%, median age at lymphoma diagnosis = 49 years in males; 42 years in females]. Most had Crohn's disease [73.7%] and were exposed to thiopurines [59.4%]. The most frequent lymphoma subtypes were diffuse large B cell lymphoma [DLBCL, 45.1%], Hodgkin lymphoma [HL, 18.8%], and follicular lymphoma [FL, 10.5%]. When matched with 365 controls, prognosis was improved in IBD patients with DLBCL compared to controls [$p = 0.0064$, hazard ratio = 0.36] or similar [HL and FL].

Conclusions: Lymphomas occurring in IBD patients do not seem to have a worse outcome than in patients without IBD. Due to the rarity of this situation, such patients should be managed in expert centres.

Key Words: Inflammatory bowel disease; ulcerative colitis; Crohn's disease; lymphoma; prognosis

1. Introduction

Lymphoma is a severe complication of autoimmune disorders[1] including Crohn's disease [CD] and ulcerative colitis [UC], which are the most common chronic and idiopathic diseases defined as inflammatory bowel diseases [IBD].[2] Patients with IBD have an increased risk of lymphoma that seems to be related to immune-modifying treatment, with a clear association with thiopurines, but very doubtful with anti-tumour necrosis factor [anti-TNF] drugs, and a lackof data with other drugs.[3] Old age [>65 years old], male gender, and use of thiopurines are critical factors associated with this risk.[3–5] About half of lymphomas developing in IBD patients arise from the gastrointestinal tract.[6,7]

In the absence of exposure to an anti-TNF and/or thiopurine, the absolute risk of lymphoma in IBD patients is quite low [0.01% per person-year] and does not exceed that of the general population.[4] Indeed, patients with IBD receiving thiopurines [azathioprine or mercaptopurine] have a statistically significantly increased risk of developing lymphoma [hazard ratio = 5.28, $p = 0.0007$].[3,8–10] Moreover, Epstein–Barr virus [EBV] infection is significantly associated with lymphoma development in patients with IBD, accounting for at least 40% of thiopurine-treated patients.[11] The extent of risk between anti-TNF therapy and the occurrence of developing lymphoma in IBD patients remains controversial.[3,12,13] This issue will be addressed by a dedicated prospective European cohort, the I-CARE project.[14]

When exposed to thiopurine therapy, the absolute risk remains low in subjects under 50 years of age and is estimated at 1 in 2000 patients per year. However, it increases in subjects over 50 years of age[8,15] and reaches 1 in 350 patients per year, which corresponds to a risk of 3% with an exposure of 10 years. Although recent data have clarified the epidemiology and risk factors of lymphoma in patients with IBD, no previous study has compared available evidence regarding detailed clinical and pathological characteristics of lymphoma occurring in patients with IBD in comparison to lymphoma occurring *de novo* [i.e. patients without IBD]. Only one French retrospective study reported a similar prognosis between lymphoma occurring in IBD vs sporadic lymphoma.[15] However, this retrospective observational study involved a limited number of patients [$n = 52$], without comparison with a control group.

We therefore investigated detailed epidemiological, clinical, pathological, and prognostic characteristics of the largest cohort of lymphomas occurring in IBD patients in the framework of a nationwide collaborative study including the GETAID [Groupe d'Étude Thérapeutique des Affections Inflammatoires du Tube Digestif] and the LYSA [Lymphoma Study Association] networks. We also performed a case-control study to assess the prognosis of the most frequent lymphoid neoplasms observed in IBD patients, compared to patients without IBD: diffuse large B cell lymphoma [DLBCL], follicular lymphoma [FL], and Hodgkin lymphoma [HL], in collaboration with the Côte d'Or registry of haematological malignancies [Burgundy, France].

2. Patients and Methods

2.1. Study design

All French centres involved in the GETAID and the LYSA networks, as well as the Brussels and Liège [Belgium] GETAID centres, retrospectively identified all patients diagnosed with lymphoid malignancies in the context of a pre-existing IBD. All patients in whom a lymphoma diagnosis was established between January 1978 and January 2022 were included, regardless of age at IBD diagnosis. Follow-up ended on August 31, 2022. Only patients who developed lymphoma at least 3 months after the diagnosis of IBD were included in our cohort. Detailed clinical and pathology data were collected for all patients through a custom-made questionnaire providing epidemiological data regarding IBD [CD vs UC, age at diagnosis, treatments] and lymphoid disorder [age at diagnosis, location, histological data, treatment, and survival data].

We also performed a case-control study for the most frequent lymphoid disorders observed in IDB patients [i.e. DLBCL, FL, and HL]. Controls were obtained from the Côte d'Or registry of haematological malignancies. The protocol was approved by the institutional review board of GETAID.

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

2.1.1. Role of funding source

No funding was needed for this retrospective study [design, data collection, data analysis, data interpretation, writing of the report]. The corresponding author had full access to all the data and had responsibility for the decision to submit for publication.

2.2. Statistical analysis

Quantitative variables are expressed by their median and interquartile range [IQR]. Qualitative variables are presented by their numbers and corresponding percentages. Overall survival [OS] was defined as the time between the date of lymphoma diagnosis and the date of death. Progression-free survival [PFS] was defined as the time between the date of lymphoma diagnosis and the date of morphological and/or histological examination documenting the progression of lymphoma or the date of death.

To minimize indication bias, cases and controls were matched using a propensity score. We fitted the following variables to a logistic regression model to compute their propensity score: gender, age at diagnosis [</≥60 years old], lymphoma subtype, year of diagnosis [1998–2010; 2010–2015; >2015], and the International Prognostic Index [IPI] [for DLBCL], follicular lymphoma international prognostic index [FLIPI] [for FL], and Ann-Arbor [for HL] indexes. We matched patients on the logit of propensity score using nearest-neighbour matching without replacement, a caliper of the 20% of the standard error of the logit, and a variable matching ratio of 1:5.[16,17] Cases matched with fewer than five controls were not excluded. To account for the correlation between cases and controls, a stratified log-rank was used to assess the absolute effect of the group [cases vs controls]. A frailty model was used to assess the relative effect of the group, using the matching identifiers as a random variable. To better understand the effect of IBD status on survival, we then performed separate frailty models on strata of available variables [age, gender, IPI/FLIPI/Ann-Arbor indexes, year of diagnosis] in DLBCL patients. We also performed a sensitivity analysis, using the same strategy but with matching on gender, lymphoma subtype, year of diagnosis [1998–2010; 2010–2015; >2015], and prognosis/staging indexes [IPI/FLIPI/Ann-Arbor], and age [±10 years] instead of the propensity score.

We considered results to be statistically significant at $p < 0.05$. All statistical analyses were performed using SAS version 9.4.

3. Results

3.1. Epidemiological and pathological data

In total, 133 patients with IBD and lymphoproliferative disorders were enrolled in the study. Most were males [83/133, 62.4% vs 50 females, 37.6%] and 98/133 had CD [73.7%] vs 35/133 [26.3%] with UC. Data on IBD treatment were available for 131/133 [98.5%] patients: 79/133 [59.4%] were exposed to thiopurine therapy [i.e. azathioprine, mercaptopurine]. Median age at IBD diagnosis was 36.0 years for males and 31.0 years for females. The median age at lymphoma diagnosis was 49.0 years in males vs 42.0 years in females. In this retrospective cohort, the most frequent lymphoma subtypes were non hodgkin lymphoma [NHL] [108/133, 81.2%], especially DLBCL [60/133, 45.1%] and FL [14/133; 10.5%]. HL represented 18.8% of our cohort [25/133]. Thirty-eight patients [28.6%] had primary digestive lymphoma. Epidemiological data for the whole cohort are presented in Table 1.

Finally, 59 of IBD patients [43 with CD, 16 with UC] with DLBCL were retained for further analysis [one DLBCL case was excluded due to missing data on lymphoma diagnosis; 16 females, 43 males]. Thirty-eight DLBCL patients [64.4%] were exposed to thiopurine therapy. The median age at DLBCL diagnosis was 48.5 years [range 21–86], and the median time of follow-up was 54.5 months [range 3–300] from the date of lymphoma diagnosis. Thirty-two cases [54%] had an IPI score >2. Ann-Arbor staging was available for 42/59 patients and was distributed as follows: stage I and II [n = 12/42, 28.6%], and stage III and IV [n = 30/42, 71.4%]. Most [46/59, 78%] received a standard of care chemotherapy regimen (R-CHOP [rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone], R-CHOEP [R-CHOP + etoposide], or R-ACVBP [rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone]).

The second most represented lymphoma subtype in our cohort was HL, with 24 cases selected for analysis [one case of lymphoma considered too old, diagnosed before 1980; ten females, 14 males]. Among them, 18 [75%] were previously exposed to thiopurine therapy, and 21/24 [87.5%] had CD. The median age at HL diagnosis was 40.0 years [range 7–69], and the median time of follow-up was 66.0 months [range 9–264]. Most patients were Ann Arbor stage IV [11/24, 45.9%], 5/24 [20.8%] were stage III, 5/24 [20.8%] were stage II, and 3/24 [12.5%] were stage I. Almost all of the HL patients [23/24, 96% with one missing data] were treated with the standard of care chemotherapy regimens (ABVD [adriamycin, bleomycin, vinblastine, and dacarbazine] or BEACOPP [bleomycin, etoposide, adriamycin, cyclophosphamide, procarbazine, and prednisone]).

The third most frequent lymphoma subtype in our cohort was FL. Fourteen cases were identified [eight females, six males] and 13 [92.3%] had CD. Among them, six [42.8%] were exposed to thiopurine treatment. The median age at FL diagnosis was 53.0 years [range 26–72], and the median time of follow-up was 62.0 months [range 10–237]. Three patients had an Ann Arbor stage IV and III [3/14, 21.4%]. Four patients had an Ann Arbor stage I and four had stage II [28.6%]. A FLIPI prognosis score was available for 10/14 FL cases. Three were FLIPI 0 [30%], three were FLIPI 1 [10%], three were FLIPI 2 [30%], two were FILIP 3 [20%] and one was FLIPI 4 [10%]. Eleven out of the 14 FL cases [78.6%] were treated with an R-CHOP standard of care chemotherapy protocol. Two patients benefitted from simple follow-up and one underwent surgery.

Details of Ann Arbor stages and IPI/FLIPI prognosis scores are provided in Supplementary Material 1, and details of IBD treatment in patients with the three most observed lymphoma subtypes in the French cohort are provided in Supplementary Material 2.

3.2. Case-control study

We investigated the three most frequent lymphoma subtypes in an IBD context, which represent 99 cases (DLBCL [n = 60/99, 60.6%]; HL [n = 25/99, 25.3% including three cases of Hodgkin lymphoma-like post-transplantation lymphoproliferative disorder [PTLD]; FL [n = 14/99, 14.1%]). Two cases [one DLBCL and one HL] were excluded because the time of lymphoma diagnosis was too early [before 1980]

Table 1. Epidemiological characteristics of patients with IBD and lymphoma.

Total	**133 [100%]**
Male	83 [62.4%]
Female	50 [37.6%]
IDB	
CD	98 [73.7%]
UC	35 [26.3%]
Median/mean age at IBD [CD and UC] diagnosis [years]	
Male	36.0/36.9
Female	31.0/37.2
IBD treatments	
Thiopurine	79 [59.4%]
Anti-TNF	46 [34.6%]
Median/mean age at lymphoma diagnosis [years]	
Male	49.0/50.0
Female	42.0/46.9
Main lymphoma subtypes	
DLBCL	60 [45.1%]
HL	25 [18.8%]
FL	14 [10.5%]
Other lymphoma subtypes	
T lymphoma	7 [5.3%]
B lymphoma	7 [5.3%]
MALT lymphoma	6 [4.5%]
Marginal zone lymphoma	5 [3.8s%]
NK/T lymphoma	3 [2.2%]
PTDL	3 [2.2%]
Polymorphic B and T lymphoproliferation	2 [1.5%]
Poppema lymphoma	1 [0.8%]

CD: Crohn's disease, DLBCL: diffuse large B cell lymphoma, FL: follicular lymphoma, HL: Hodgkin's lymphoma, IBD: inflammatory bowel disease, MALT: mucosa-associated lymphoid tissue, PTDL: post-transplant lymphoproliferative disorder, UC: ulcerative colitis.

or missing. Among them, matching on the propensity score estimated with the five criteria mentioned above (i.e. gender, age at diagnosis [</≥60 years old], lymphoma subtype, year of diagnosis [1998–2009; 2010–2015; >2015] and IPI/FLIPI/Ann-Arbor indexes]) was successful for 82 cases. They were matched with 365 controls [217 DLBCL, 46 FL and 102 HL controls]. Therefore, a total of 447 patients were included in the survival data analysis. There was few differences between cases and controls after matching on the available variables. Details are provided in Table 2. The estimated median of survival was 59.5 months [IQR: 36.7–113.4] for cases and 41.5 months [IQR: 25.2–88.8] for controls.

OS at 1 and 5 years for all cases were respectively 96% (95% confidence interval [CI] 92.0–100%) and 83% [95% CI 74.3–91%] vs 90% [95% CI 87–93.2%] and 69% [95% CI 62.8–74.9%] for controls [stratified log-rank: $p = 0.0188$] [Figure 1]. PFS at 1 and 5 years for the most represented cases were 91% [95% CI 84.5–97.4%] and 78% [95% CI 67.9–88%] respectively, compared to 88% [95% CI 84.6–91.3%] and 67.5% [95% CI 61.6–73.5%] for the control group [stratified log-rank: $p = 0.0832$]. In our cohort of patients with IBD and lymphoma, the reported causes of death were almost exclusively related to the course of lymphoma [85%] [i.e. poor course of the disease, clinical deterioration, no toxic deaths attributable to lymphoma treatment, missing data: $n = 3$].

Among the 59 DLBCL cases, 48 were matched with 217 controls. OS at 1 and 5 years for cases were respectively 95.8% [95% CI = 90.1–100%] and 77.8% [95% CI = 63.7–91.8%] vs 84.3% [95% CI = 79.4–89.1%] and 53.3% [95% CI = 45–61.6%] for controls [stratified log-rank: $p = 0.1572$] [Figure 2]. The frailty model showed a significant association between pre-existing IBD and a better prognosis of lymphoma ($p = 0.0064$, hazard ratio [HR] = 0.36 [95% CI = 0.17–0.75]). PFS at 1 and 5 years for cases were 88.9% [95% CI = 79.7–98.1%] and 71% [95% CI = 56–86%] respectively, compared to 82% [95% CI = 76.8–87.1%] and 58.4% [95% CI = 50.5–66.3%] for controls. In DLBCL patients, when comparing HR associated with pre-existing IBD between strata of available variables, no differences between estimates were observed,

Table 2. Patient characteristics after matching with controls.

	Cases [$n = 82$]	Controls [$n = 365$]	Total [$n = 447$]
Gender			
Male	52 [63.4%]	226 [61.9%]	278 [62.2%]
Female	30 [36.6%]	139 [38.1%]	169 [37.8%]
Mean age at lymphoma diagnosis [years]			
<60	65 [79.3%]	229 [62.7%]	294 [65.8%]
≥60	17 [20.7%]	136 [37.3%]	153 [34.2%]
Lymphoma subtypes			
DLBCL	48 [58.5%]	217 [59.5%]	265 [59.3%]
HL	10 [12.2%]	46 [12.6%]	56 [12.5%]
FL	24 [29.3%]	102 [28.0%]	126 [28.2%]
Ann Arbor stage			
I and II	39 [47.6%]	155 [42.5%]	194 [43.4%]
III and IV	43 [52.4%]	210 [57.5%]	253 [56.6%]
Survival data			
Alive	70 [85.4%]	190 [76.0%]	336 [75.2%]
Deceased	12 [14.6%]	60 [24,0%	111 [24.8%]
Time of lymphoma diagnosis			
1998–<2010	13 [15.9%]	65 [17.8%]	78 [17.5%]
2010–2015	30 [36.6%]	144 [39.5%]	174 [38.9%]
>2015	39 [47.6%]	156 [42.7%]	195 [43.6%]

DLBCL: diffuse large B cell lymphoma, FL: follicular lymphoma, HL: Hodgkin lymphoma.

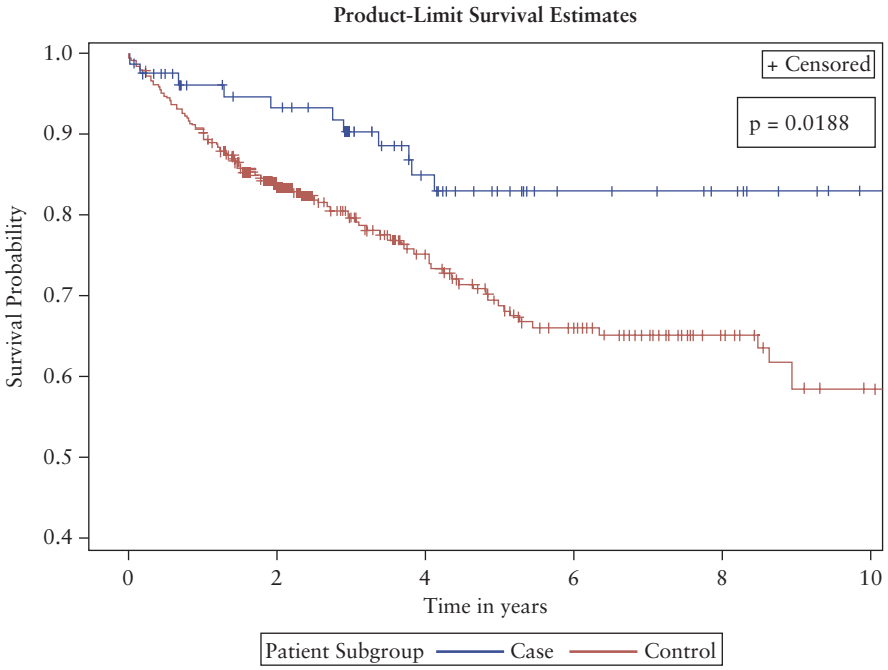

Figure 1. Overall survival curves for cases and controls in the total population [three main lymphoma subtypes].

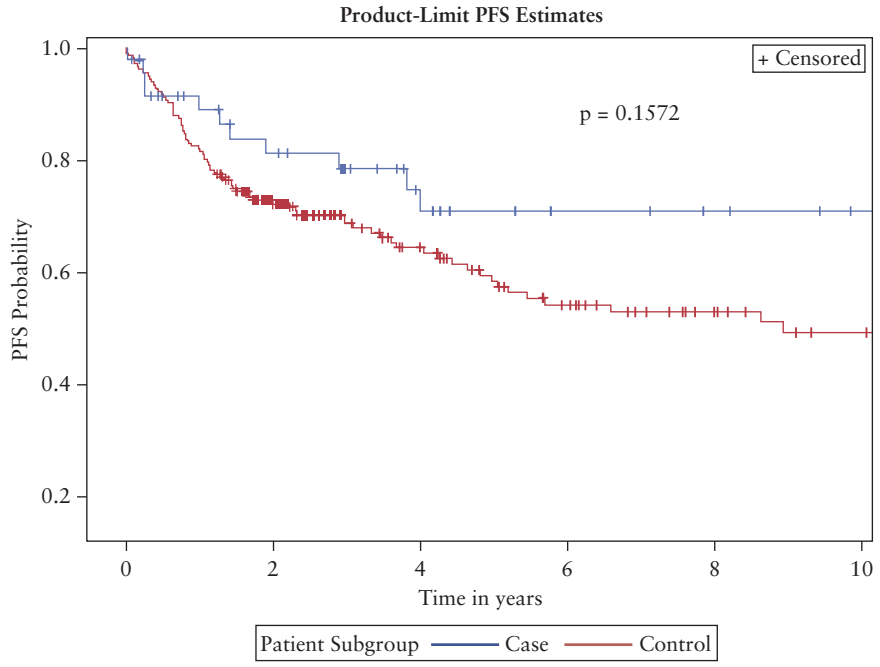

Figure 2. Overall survival curves for diffuse large B cell lymphoma in cases and controls.

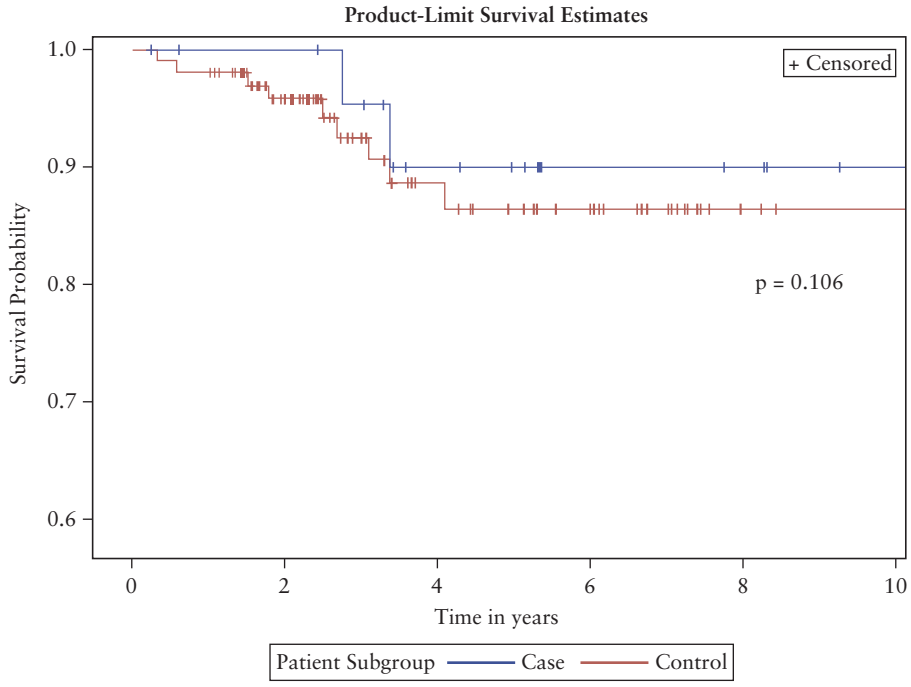

Figure 3. Overall survival curves for Hodgkin lymphoma in cases and controls.

except for age: HR was lower for patients ≥60 years old (0.30 [95% CI = 0.07–1.24]), than for their younger counterparts (0.54 [95% CI = 0.22–1.32]).

The 24 HL cases were matched with 102 controls. OS at 1 year was 100% in HL cases vs 98% in matched controls [95% CI = 95.3–100%]. OS at 5 years was 90% in cases [95% CI = 76.7–100%] vs 81.8% [95% CI = 71.8–912%] in matched controls [stratified log-rank: $p = 0.1059$] [Figure 3]. There was no association between pre-existing IBD and a better prognosis of HL ($p = 0.6828$, HR = 0.76 [0.2–2.9]).

Ten FL cases were matched with 46 controls. OS at 1 year was 90% in FL cases [95% CI = 71.4–100%] vs 100% in matched controls. OS at 5 years was 90% in cases [95% CI = 71.4–100%] vs 88% [95% CI = 76.5–100%] in matched controls [stratified log-rank: $p = 1$]. The sample size was not sufficient to provide a reasonable estimation of the HR.

Sensitivity analysis, using matching on each variable instead of a propensity score, produced similar estimates with a lower sample size [70 cases, 250 controls]. The HR estimate of pre-existing IBD from the frailty model was similar to the main analysis (0.44 [95% CI = 0.19–0.98]) for DLBCL

patients. HR estimates for other subpopulations, as well as all stratified log-rank estimates, remained non-significant.

4. Discussion

In patients with IBD, lymphoproliferative disorders are a rare but unpredictable and deadly complication. That absolute risk has been estimated at 1 in 2000 patientsd per year when ≤50 years old and 1 in 350 patients per year when >50 years old.[15] Although the risk factors associated with the development of lymphoma in this population have been identified,[3,5] limited data have been reported regarding their epidemiological, clinical, and prognostic characteristics. Only two papers have recently assessed those uncertainties. One original article reported 52 cases of lymphoma in patients with IBD, among them 34 aggressive lymphomas [17 DLBCL and 17 HL] and 20 of them were primary digestive lymphoma.[15] The authors observed that PFS at 3 years was 94% for DLBCL, 91% for FL, and 70% for HL, close to those observed in studies with non-IBD patients, but no comparison to a control group was performed [OS was not reported in their study]. A systematic review described epidemiological data from 589 lymphomas [from 11 studies] occurring in patients with IBD.[6] DLBCL and FL were the most commonly represented NHL in patients with IBD [30% and 13% respectively].

To our knowledge, we have reported here the largest series of lymphomas in IBD patients, with 133 cases. The three main subtypes of lymphoproliferative disorders were DLBCL, FL, and HL, representing 45.1, 10.5, and 18.8% of our whole cohort, respectively. These proportions appear to be comparable to the distribution of cases of lymphoma observed in the general population.[18] Moreover, our observations confirm that lymphoma with primary digestive origin are widespread in this particular population and affects one-quarter of patients.

Given the small number of some lymphoma subtypes, we focused on the three most represented lymphoma subtypes to perform statistical comparison through a case/control study. Cases were matched with five controls thanks to data from the Côte d'Or registry of haematological malignancies [part of the French national cancer registry network], using two different strategies.

We therefore provide for the first time data regarding the prognosis of the main lymphoma subtypes occurring in IBD patients, in comparison with the general population.

As mentioned previously,[15] we observed that the prognosis of lymphoproliferative disorders occurring in patients with IBD was either improved in IBD patients or similar compared to controls [according to lymphoma subtype]. Indeed, we report in our whole case population a PFS and OS at 5 years of 78 and 83% respectively vs 67.5 and 69% in sporadic controls [$p < 0.05$]. This was mainly seen for the DLBCL subgroup with OS at 5 years of 77.8% in cases vs 53.3% in sporadic controls.

At present, there are no data in the literature providing a formal explanation for these significant and striking differences in survival data. We initially suspected a possible difference in age between cases and controls [propensity matching on a recategorized variable: < or ≥60 years]. Indeed, in our case series, the median age at diagnosis of lymphoma was quite young [49 years for men, 42 years for women], and therefore the cut-off of 60 years may not be appropriate [1:5 matching was not feasible for a lower age]. However, sensitivity analysis using exact matching [with an age tolerance of 10 years] produced almost the same results. Thus, age is probably not the main explanatory factor between survival and pre-existing IBD. We also observed a possible interaction between age and IBD status [HR lower in older DLBCL patients], but it was not possible to formally test this interaction due to the matching on age.

Another explanation could be that all the cases included in this retrospective study came from GETAID centres, which were university hospital reference care centres, in contrast to the patients from the registry. A recruitment bias is possible. Regarding the tolerance of chemotherapy treatments, we did not find any significant and limiting toxic event that could have altered the oncological management of patients with lymphoma and IBD.

Our study has many strengths, especially the size and the multi-centre nature of the cohort. Likewise, we report the specific treatments for lymphoma received by the patients in our cohort: they mostly followed the recommendations. Moreover, the median follow-up after lymphoma diagnosis is significant, at >4 years. Our cohort could therefore constitute a representative sample. However, our study has some limitations mainly due to its retrospective design and the lack of a centralized review of lymphoma cases. Some of the data were not sufficient in the retrospective collection of files and therefore could not be exploited, in the first instance the prevalence of EBV and additional demographic data [i.e: tobacco use, concomitant disease, body mass index]. Recruitment bias also cannot be eliminated. Although our study has clarified the prognostic factors and highlighted the good prognosis of lymphomas occurring in IBD, many uncertainties remain. It is still unclear whether *de novo* lymphoma or lymphoma arising in IBD patients [exposed or not to thiopurine and/or anti-TNF therapy] are distinct entities. Indeed, no study has focused on molecular and genomic alterations of lymphoma occurring in patients with IBD, which might be different especially due to microenvironmental remodelling [immunosuppressive therapy, chronic inflammation, microbiota].

In conclusion, this retrospective multicentre study is the largest reported to date, focusing on clinical characteristics of lymphoma occurring in patients with IBD. Focusing on the three most common lymphoma subtypes occurring in IBD patients [DLBCL, HL, and FL], we have demonstrated for the first time that lymphoma prognosis was either improved in IBD patients or similar to controls. Due to the complex management of these patients, it seems likely that most will be managed in expert centres. Despite recent satisfactory clinical descriptions of lymphomas occurring in patients with IBD, the understanding of oncogenetic events remains limited and has not been fully elucidated. Further studies are required to better define lymphoma characteristics and lymphomagenesis in patients with IBD.

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None.

Conflict of Interest

DL received counselling, boards, transports, and/or fees from Abbvie, Amgen, Celltrion, Ferring, Galapagos, Janssen, Lilly, MSD, Novartis, Pfizer, Prometheus, Roche, Takeda,

and Tillots. JB received consulting fees from AstraZeneca and lecture fees from Novartis, Abbvie, and Janssen. LB received consulting fees from BMS, Janssen, Nordic Pharma, and Mylan; lecture fees from Abbvie, BMS, Janssen, MSD, Ferring, and Takeda; and research support from Abbvie, Celltrion, Ferring Pharmaceuticals, Hospira-Pfizer, Janssen, MSD, Mylan, Takeda, and Tillots. LPB received consulting fees from AbbVie, Alimentiv, Alma Bio Therapeutics, Amgen, Applied Molecular Transport, Arena, Biogen, BMS, Celltrion, CONNECT Biopharm, Cytoki Pharma, Enthera, Ferring, Fresenius Kabi, Galapagos, Genentech, Gilead, Gossamer Bio, GSK, HAC-Pharma, IAG Image Analysis, Index Pharmaceuticals, Inotrem, Janssen, Lilly, Medac, Mopac, Morphic, MSD, Norgine, Novartis, OM Pharma, ONO Pharma, OSE Immunotherapeutics, Pandion Therapeutics, Pfizer, Prometheus, Protagonist, Roche, Sandoz, Takeda, Theravance, Thermo Fisher, Tigenix, Tillots, Viatris, Vifor, Ysopia, and Abivax; and grants from Takeda, Fresenius Kabi, Celltrion; Lecture: Galapagos, AbbVie, Janssen, Genentech, Ferring, Tillots, Celltrion, Takeda, Pfizer, Sandoz, Biogen, MSD, Amgen, Vifor, Arena, Lilly, Gilead, Viatris, and Medac. MMa received consulting fees from Janssen and Abbie. PF received counselling, boards, transports, and/or fees from Abbvie, Astrazeneca, Gilead, Janssen, Beigene, and Lilly. SN received counselling, boards, transports, and/or fees from Abbvie, Janssen, Biogen, Celltrion, Ferring, Galapagos, Novartis, Pfizer, Takeda, and Tillots Pharma. MMu, AG, SW, CT, GC, AA, SV, YB, CMa, CMi, XH, GS, DF, PS, MMa, and PF have no conflict of interest to declare.

Author Contributions

LPB and PF conceived the study. MMu collected all data. MMu wrote the manuscript. JB, AG, SW, CT, SN, GC, AA, DL, SV, YB, CMa, CMi, XH, GS, DF, PS, LP, MMa, PF, and LPB critically reviewed the content of the paper. Statistical analysis: AG, SW, and MMa. All authors discussed the results and contributed to the final manuscript. Review and approval of the manuscript: all of the authors.

Supplementary Data

Supplementary data are available online at *ECCO-JCC* online.

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