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RESEARCH LETTERS

Incidence and Survival in Patients With Enteropathy-associated T-Cell Lymphoma: Nationwide Registry Studies From England and Denmark

Enteropathy-associated T-cell lymphoma (EATL) is a rare and highly aggressive T-cell non-Hodgkin lymphoma[1] that is strongly associated with refractory celiac disease and possibly inflammatory bowel disease (IBD). The incidence and prevalence of both celiac disease[2] and IBD[3] have been rising around the world for several decades, including in both England and Denmark. Potential drivers of EATL are the antigen-driven proliferation of intravillous T cell from celiac disease and chronic inflammation in IBD, so it is important to understand if changes in these diseases are altering clinical presentations of EATL and its survival.

We therefore quantified the contemporary incidence and survival of EATL from England and Denmark. We identified people with EATL using the International Classification of Diseases for Oncology, third edition, morphology code 97173 for neoplasms diagnosed between January 1, 2013 and December 31, 2019 in England, and January 1, 2004 to December 31, 2020 in Denmark. We calculated incidence, survival, and mortality hazard ratios using standard statistical techniques (See Supplementary Methods for details).

We identified 172 patients with EATL diagnosed in 2013–2019 in England and 39 in 2004–2020 in Denmark. The average age at diagnosis was similar in both countries (~66–68 years), but more men (63%) than women (37%) were diagnosed in England, with the reverse in Denmark (Table 1). Approximately half of both cohorts (England, 52%; Denmark, 41%) had celiac disease and 6% and 8% had IBD recorded in England and Denmark, respectively (Table 1). Overall crude incidence was similar between the 2 countries: 0.45 (95% confidence interval [CI], 0.38–0.51) and 0.41 (95% CI, 0.29–0.56) per million population per year in England and Denmark, respectively. Ages standardized to the European 2013 population rates were 0.48 (95% CI, 0.41–0.56) and 0.44 (95% CI, 0.30–0.58) per million population per year, respectively.

Supplementary Table 1 shows the rates and adjusted incidence rate ratios for the available characteristics in both countries. Overall, the incidence of EATL increased in older age groups, was greater in men in England, but was similar in men and women in Denmark. When fitted as continuous variables, there were no clear trends over the calendar year.

Median survival was approximately 6–7 months in both cohorts, and 1- and 5-year survival rates were 35% (95% CI, 29–43) and 10% (95% CI, 6–18) in the English cohort and 38% (95% CI, 24–53) and 20% (95% CI, 9–33) in the Danish cohort. The 3-year survival rate did not vary greatly by age, region, and deprivation in England, but women had better overall survival than men. In Denmark, men had similar 3- and 5-year survival rates to women. In England, better 1-year survival rates were observed in patients selected for higher levels of therapy: from small-bowel surgery alone (overall survival, 28%; 95% CI, 18–44), small-bowel surgery and chemotherapy (overall survival, 50%; 95% CI, 39–65), to small-bowel surgery and stem cell transplant (overall survival, 77%; 95% CI, 62–97), noting that the latter group had survival estimated from date of the transplant.

In England, once age, sex, region, and deprivation were adjusted for, those who had celiac disease had approximately a 35% reduction in their mortality hazard (adjusted hazard ratio, 0.65; 95% CI, 0.45–0.93) compared with those without celiac disease. The same observation was made for those with celiac disease in Denmark (adjusted hazard ratio, 0.58; 95% CI, 0.26–1.32) (Supplementary Table 2).

In summary, in both England and Denmark, the overall incidence rates of EATL and survival after diagnosis were very similar. Of note, approximately 50% of all cases of EATL have a coexisting diagnosis of celiac disease and 6%–8% have coexisting IBD. People with celiac disease fare better, as do those who have small-bowel surgery at diagnosis. The best survival rates were found in a small minority of patients with EATL (n = 23, 13%) who were well enough to have both small-bowel surgery and stem cell transplantation.

The literature describing the epidemiology of EATL is scarce, and besides the older population-based studies from the United States[4] and the Netherlands,[5] there are only regional-based studies from the United Kingdom with which to make comparisons.[6,7] These latter 2 studies estimated the overall incidence in their regions to be around 1 per million, like the Dutch study, but were both small with considerable uncertainly in their estimates. That they observed double the incidence rates compared with our current analysis is probably due to a combination of random error from a smaller sample size, ascertainment or referral bias, and slightly different inclusion criteria in these studies.[6,7] Overall survival in our cohorts were poor and consistent with previously reported studies, with most succumbing to the disease within 1 year, and we confirm results from smaller studies suggesting that the small fraction of patients able to receive stem cell transplantation has better outcomes.[7,8] The better survival with increasing levels of therapy likely reflects the clinical judgement involved in case selection for these therapies, but without detailed performance status in our data we were unable to examine this. A series of 61 patients from the Netherlands suggested

Abbreviations used in this paper: CI, confidence interval; EATL, enteropathy-associated T-cell lymphoma; IBD, inflammatory bowel disease.

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Table 1. Baseline Characteristics of the Cohort of People With Enteropathy-associated T-Cell Lymphoma Using the International Classification of Diseases for Oncology, Third Edition, Code 97173

Category	England (n = 172)	Denmark (n = 39)
Mean age, y (95% confidence interval)	66 (44–89)	68 (65–72)
Male sex	108 (63)	18 (46)
Female sex	64 (37)	21 (54)
Stage, low	47 (27)	10 (26)
Stage, high	81 (47)	18 (46)
Stage, missing	44 (26)	11 (28)
Median Charlson score (IQR)	0 (0, 0)	0 (0, 0)
Ethnicity, white	160 (93)	N/A
Ethnicity, other	12 (7)	N/A
Most deprived	34 (20)	N/A
Quintile 2	31 (18)	N/A
Quintile 3	33 (19)	N/A
Quintile 4	39 (23)	N/A
Least deprived	35 (20)	N/A
Stem cell transplant	30 (17)	N/A
Chemotherapy[a] CHOP[a] Intensive chemotherapy[a]	89 (52) 80 (47) 9 (5)	N/A N/A N/A
No relevant chemotherapy[a]	83 (48)	N/A
Celiac disease	89 (52)	16 (41)
Inflammatory bowel disease	11 (6)	3 (8)
Small-bowel surgery	110 (64)	10 (26)
Median time to chemotherapy, days from diagnosis (IQR)[b]	40 (27, 55)	NA
Median time to transplant, days from diagnosis (IQR)[b]	211 (190, 246)	NA
Median time to surgery, days from diagnosis (IQR)[b]	0 (0, 0)	0 (–20, 1)
Median time to celiac disease, days from diagnosis (IQR)	–26 (–53, –4)	–340 (–1711, 48)
Median time Inflammatory bowel disease, days from diagnosis (IQR)	–53 (–61, –30)	–182 (–704, 2067)
Died	144 (84)	33 (85)

NOTE. Values are n (%) unless otherwise defined. IQR, interquartile range; N/A, not available in Danish data.
[a]Chemotherapy includes CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone [plus variants]) or intensive chemotherapy; no relevant chemotherapy includes palliative chemotherapy, stem cell chemotherapy, and other chemotherapy not relevant to enteropathy-associated T-cell lymphoma or no chemotherapy.
[b]For those who received chemotherapy, a stem cell transplant, or had a surgery.

those who have a concurrent diagnosis of celiac disease and EATL, as was the case for most patients in our series, have better outcomes.[9] This contrasts with a report from the International Peripheral T-Cell Lymphoma Project[10] on 62 patients where celiac disease was associated with worse progression-free survival.

Of note is our observation that a higher than expected proportion of cases of EATL have a concurrent diagnosis of IBD, with a background prevalence of IBD in both countries of around 1%. EATL occurring in people with IBD has been observed previously in a few case reports; however, misdiagnosis of IBD might explain a proportion of IBD cases and miscoding (of both IBD and celiac disease) might theoretically explain a few. Nevertheless, it is clearly possible that site-specific chronic inflammation, sustained pharmacologic immunosuppression, or both could contribute to an increased risk of EATL in IBD, as seen in other non-Hodgkin lymphoma cases.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org and at https://doi.org/10.1053/j.gastro.2023.06.003.

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Acknowledgments
The study protocol for the English data was reviewed by an NHS Research Ethics Committee (REC reference: 21/YH/0128) and was approved by the Health Research Authority Approval, which is the process for research in the NHS in England. According to Danish law, studies based entirely on data from registries, such as ours, do not need informed consent from patients. Permissions to conduct the study were obtained from the Danish Data Protection Agency and the Danish Health Data Authority, which also extracted the data and gave us access to it.

CRediT Authorship Contributions
Joe West, BMedSci, BM, BS, MSc, PhD, PgDiploma, MSc (Conceptualization: Lead; Data curation: Lead; Formal analysis: Lead; Investigation: Lead; Methodology: Lead; Project administration: Lead; Software: Lead; Supervision: Lead; Validation: Lead; Visualization: Lead; Writing – original draft: Lead; Writing – review & editing: Lead).

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Conflicts of interest
The authors disclose no conflicts.

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Data Availability
This work uses data provided by patients and collected by the NHS as part of their care and support. The data are collated, maintained, and quality ensured by the National Cancer Registration and Analysis Service, which is part of the Health and Social Care Information Center (NHS Digital). Access to data was facilitated by the UK Health Security Agency (UKHSA) Office for Data Release. We do not own these data and hence are not permitted to share them in the original form https://www.ndrs.nhs.uk/odr/. The Danish data can only be accessed through an encrypted virtual private network with the above approvals in place and therefore cannot be shared.

Supplementary Methods

Data Sources

In England, data from the National Cancer Registration Dataset was used.[1] The National Cancer Registration Dataset holds the population-based national cancer registry for England and is linked to other datasets for analysis purposes, including Hospital Episode Statistics[2] and the Systemic Anti-Cancer Therapy dataset.[3] To assess deprivation, it is linked to the Index of Multiple Deprivation, which is the official measure of relative deprivation for small areas in England. For allocation of National Health Service region and deprivation, we used the postal code of the residence of the patient at the time of diagnosis. In Denmark, the National Cancer Registry[4] and National Patient Registry[5] were used. Further details of the validity of data and diagnoses in both datasets are cited elsewhere.[6–11]

Available Data and Variable Definitions

In the English data, there was information available on sociodemographics, Charlson Comorbidity Index score[12] in the 2-year period ending 3 months before diagnosis, deprivation quintile, National Health Service region, treatment, operations, procedures, and death. Most, but not all, of this information was also available in the Danish data. In both countries we defined celiac disease and IBD using International Classification of Diseases, 10th edition and stage of EATL using the Ann Arbor classification. In the English data, diagnostic International Classification of Diseases, 10th edition codes were only available when a person was admitted to the hospital or for a day case procedure,[2] whereas in Danish data diagnostic coding of outpatient visits is also available.[5] This means that for the diagnoses of celiac disease and IBD in England, the date of recording represents either prevalent celiac disease diagnosed some time previously as an outpatient or coincident disease, but we are unable to know which. In the Danish data, the dates of recording for celiac disease and IBD represent dates of diagnosis.

For small-bowel surgery and stem cell transplant, we used Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures, version 4 codes for the English data and NOMESCO Classification of Surgical Procedures codes for the Danish data. For stem cell transplant we included procedures that occurred 90 days before or up to 730 days after diagnosis of EATL. For small-bowel surgery, we included procedures that occurred before or up to 90 days after diagnosis of EATL. In the English data, we defined first chemotherapy treatment as either cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP and/or variations) or intensive chemotherapy or as no relevant chemotherapy. The latter group included agents used for palliation, other reasons, or receipt of no chemotherapy. Data on chemotherapy were not available in the Danish data. Where other data are not available in Denmark, this is listed as N/A in the tables.

Statistical analysis

Incidence. Crude and directly age-standardized incidence rates per million persons per year were calculated. The total at-risk population was defined as the English Office for National Statistics midyear population estimates for age, sex, region, and deprivation quintile and the annual Danish population at midyear from the Danish Civil Registration System. Age-standardized incidence rates were age-adjusted to the 2013 European Standard Population. Crude and adjusted incidence rate ratios were calculated to compare incidence between groups using Poisson regression, and calendar time trends were assessed.

Survival. Overall survival was calculated from the date of diagnosis of EATL to the earliest of date of death from any cause with censoring when a person was lost to follow-up (emigrated) or when follow-up ended, which was in England January 5, 2021 and in Denmark August 31, 2022. For those who had a small-bowel surgery followed by a stem cell transplant, a landmark analysis was used whereby survival was calculated from the date of stem cell transplant. Overall 5-year survival was estimated using the Kaplan-Meier method (in the English cohort, because of a shorter follow-up we estimated 3-year survival when stratified by baseline characteristics, whereas in the Danish cohort, we estimated 3- and 5- year survival). A Cox proportional hazards regression model adjusting (where variables were available) for age, sex, deprivation, and region was fitted to estimate adjusted hazard ratios for celiac disease and small-bowel surgery.

Statistical software. All statistical analyses were performed using R (2022; R Foundation for Statistical Computing) and/or Stata (release 17; StataCorp).

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Supplementary Table 1. Number of Cases, Populations, Rates per Million, Crude and Adjusted Incidence Rate Ratios by Various Characteristics in the English and Danish Cohorts

Category	Rate (per million)	95% CI	Adjusted incidence rate ratios[a]	95% CI
English cohort				
Sex				
Male	0.57	0.46–0.67	Reference	
Female	0.33	0.25–0.41	0.53	0.39–0.72
Age groups				
0–50 y	0.07	0.04–0.11	Reference	
50–55 y	0.37	0.14–0.61	5.16	2.29–10.97
55–60 y	0.72	0.38–1.06	9.87	5.04–19.24
60–65 y	1.15	0.69–1.61	15.93	8.67–29.80
65–70 y	1.37	0.86–1.88	19.11	10.64–35.21
70–75 y	1.70	1.08–2.32	23.71	13.25–43.57
75–80 y	1.88	1.13–2.64	26.63	14.48–49.86
80+	1.17	0.68–1.66	17.34	9.29–32.81
Calendar year				
2013	0.37	0.21–0.53		
2014	0.41	0.24–0.57		
2015	0.40	0.23–0.57		
2016	0.49	0.30–0.67	1.04[b]	0.96–1.12
2017	0.45	0.27–0.63		
2018	0.52	0.33–0.71		
2019	0.48	0.30–0.66		
National Health Service Region				
London	0.29	0.16–0.43	Reference	
Southeast	0.39	0.24–0.55	0.98	0.53–1.85
Southwest	0.41	0.21–0.62	0.94	0.47–1.85
East of England	0.63	0.39–0.86	1.55	0.86–2.87
Midlands	0.36	0.22–0.50	0.88	0.48–1.63
Northeast and Yorkshire	0.59	0.39–0.78	1.40	0.80–2.54
Northwest	0.51	0.31–0.72	1.25	0.68–2.34
Index of multiple deprivation quintile				
1 (most deprived)	0.44	0.29–0.59	Reference	
2	0.39	0.25–0.53	0.83	0.50–1.36
3	0.42	0.28–0.57	0.77	0.47–1.27
4	0.51	0.35–0.67	0.87	0.55–1.40
5 (least deprived)	0.47	0.31–0.62	0.78	0.48–1.27
Danish cohort				
Sex				
Male	0.38	0.23–0.60	0.97	0.51–1.82
Female	0.44	0.27–0.67	Reference	
Age group				
0–50 y	0.02	0.00–0.09	Reference	
50–55 y	0.31	0.04–1.11	18.52	1.68–204.26
55–60 y	0.97	0.35–2.10	58.02	6.98–481.90
60–65 y	1.19	0.48–2.45	71.43	8.79–580.56
65–70 y	0.96	0.31–2.25	58.24	6.80–498.66
70–75 y	2.37	1.14–4.36	143.95	18.41–1125.66
75–80 y	0.98	0.20–2.88	59.41	6.18–571.52
80+	1.24	0.40–2.90	74.60	8.70–639.81
Calendar year				
2004	0.19	0.00–1.03		
2005	0.74	0.20–1.89		
2006	0.37	0.04–1.33		
2007	0.37	0.04–1.33		
2008	0.18	0.00–1.02		
2009	0.36	0.04–1.31		
2010	0.90	0.29–2.11		
2011	0.36	0.04–1.30		
2012	0.18	0.00–1.00	0.99[c]	0.93–1.05
2013	0.54	0.11–1.56		
2014	0.18	0.00–0.99		
2015	0.35	0.04–1.28		

Supplementary Table 1. Continued

Category	Rate (per million)	95% CI	Adjusted incidence rate ratios[a]	95% CI
2016	0.70	0.19–1.79		
2017	0.35	0.04–1.26		
2018	0.69	0.19–1.77		
2019	0.00	0.00–0.64		
2020	0.52	0.11–1.51		

[a]Poisson regression model mutually adjusted for all variables in the table.
[b]Fitted as a continuous variable to enable comparison with the Danish cohort.
[c]Fitted as a continuous variable because of small numbers.

Supplementary Table 2. Adjusted Hazard Ratios for Overall Mortality for Available Characteristics in England and Denmark

	England		Denmark	
Predictors	Hazard ratios[a]	95% CI	Hazard ratios[a]	95% CI
Male	Reference		Reference	
Female	0.61	0.42–0.88	1.44	0.65–3.20
Age 0–55 y	0.75	0.41–1.39	1.91	0.48–7.63
Age 55–65 y	Reference		Reference	
Age 65–75 y	1.24	0.76–2.02	1.33	0.54–3.25
Age 75–120 y	1.17	0.70–1.95	3.20	1.15–8.89
London	Reference			
Southeast	2.56	1.20–5.45		
Southwest	1.55	0.70–3.47		
East of England	2.33	1.11–4.88		
Midlands	1.35	0.64–2.85		
Northeast and Yorkshire	2.29	1.13–4.64		
Northwest	1.37	0.66–2.88		
1 (most deprived)	Reference			
2	0.76	0.43–1.35		
3	0.80	0.44–1.47		
4	0.90	0.53–1.53		
5 (least deprived)	0.72	0.41–1.25		
No celiac disease	Reference		Reference	
Celiac disease	0.65	0.45–0.93	0.58	0.26–1.32
No small-bowel surgery	Reference		Reference	
Small-bowel surgery	0.70	0.47–1.02	1.11	0.45–2.75
Observations	170		39	

[a]Cox regression model estimating hazard ratios mutually adjusted for all available variables in the table per country.