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LETTER TO THE EDITOR

Overall survival and registration of cutaneous T-cell lymphoma patients in Sweden: a multi-center cohort and validation study

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Introduction

Primary cutaneous T-cell Lymphoma (CTCL) is a group of rare non-Hodgkin lymphomas characterized by malignant T cells that are initially only present in the skin. Mycosis fungoides (MFs) represent the most common primary CTCL accounting for nearly 60% of all cases with an incidence of 0.2–0.6 cases/100,000 person years in Europe and the USA [1–4]. MF often has an indolent clinical course characterized by superficial skin patches and/or elevated plaques. However, for unknown reasons some patients develop a more aggressive form of the disease with skin tumors, erythroderma, and/or extracutaneous involvement [5]. Consequently, the prognosis of MF is often favorable, but may still vary considerably among patients and is dependent on the stage of the disease [6]. Early-stage disease (stage IA–IIA) generally has a favorable prognosis with a 5-year disease-specific survival of 89%–98%, while advanced-stage MF (IIB-IV) has a worse prognosis with a 5-year disease-specific survival reported to range between 18 and 67% [7,8]. Population-based data on the overall survival (OS) among CTCL patients are mostly limited to studies that are small, old, or with short follow-up considering the often indolent course of CTCL [9–11].

Population-based registers are important and relatively non-biased data sources for both clinical and research purposes. The Swedish Cancer Register (SCR) is a nation-wide register with mandatory recording of all newly diagnosed cancer patients. The Swedish Lymphoma Register (SLR) was initiated in the year 2000 to complement SCR with more detailed lymphoma-specific data for follow-up of quality of care. SLR thus records data on adult (>18 years) lymphoma patients including lymphoma subtype, stage, primary treatment, treatment response, and survival.

To avoid selection bias in register studies, it is important to ensure that the levels of coverage and completeness of a register are sufficient. According to the yearly report of the SLR, the completeness of the registry regarding all lymphoma patients is >95%, when compared with cases registered in the SCR [12]. However, the level of completeness for specific lymphoma subtypes, including CTCLs, has so far not been described. We hypothesized that CTCL patients may be underreported into the SLR, since they are often managed at dermatology clinics and not at oncology or hematology clinics where most other lymphoma patients are treated. We also hypothesized that patients with early-stage disease and hence longer survival time may have been registered to a lower extent. To investigate these questions, we have performed the first validation of the data quality of national registration of CTCLs in Sweden using medical records as the gold standard. In addition, we have performed a comprehensive evaluation of patient characteristics and OS in a large CTCL cohort.

Patients and methods

Patients with CTCL treated at the university hospitals of two major county councils in Sweden: the Karolinska University Hospital (KUH) in Stockholm county and the Uppsala University Hospital (UUH) in Uppsala county were included in this study. Since the treatment of CTCL in these counties is highly centered to university clinics, the coverage of incident cases from the geographical catchment areas is likely high.

Completeness and timeliness of the SLR registration were investigated by CTCL subtype, sex, age, and stage. In addition, OS was estimated for the entire study population and for registered versus unregistered MF and Sézary syndrome (SS) patients based on the survival data collected from patient medical records.

The Swedish Ethical Review Authority approved the study.

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Study population

The study population consisted of patients diagnosed with CTCL between the years 2000 and 2017 at KUH and between the years 2000 and 2018 at UUH. Index patients were identified through the medical record systems at the dermatology, hematology, and oncology clinics using the International Classification of Diseases 10th revision (ICD-10) codes C84.0 (MF), C84.1 (SS) and C84.8 (CTCL, unspecified). Since CTCL is a heterogeneous group of rare diseases where many subtypes lack specific ICD-10 codes or are frequently misdiagnosed, the additional codes C84.4 (Peripheral T-cell lymphoma, not classified), C84.5 (other mature NK-T cell lymphoma) and C84.9 (mature NK-T cell lymphoma, unspecified) were also included in the initial search. The diagnosis was verified in the chart, non-CTCL patients were excluded and relevant clinical information was retrieved following written informed consent from live patients (Supplementary Figure 1). Patient data from the medical records were linked to the SLR by the unique Swedish personal identity number, and we noted if the patients were registered in the SLR or not. Two patients were treated at both hospitals but were only counted once.

Statistical analysis

Data were summarized using descriptive statistics of patient subpopulations. Chi-square test was used for categorical data to compare groups. OS probabilities were calculated using the Kaplan–Meier method and tested for significance using the log-rank test. OS was defined as the time from the date of diagnosis until death, with administrative censoring at last follow-up. Univariable and multivariable Cox proportional hazard models were used to estimate the association of clinical variables and SLR registration with OS. Cox regression analyses were performed in SAS software. P-values were two-sided and <0.05 was considered statistically significant.

Results

Study population characteristics

The final study population consisted of 127 patients (KUH: $n = 101$; UUH: $n = 26$). The patients were categorized in two subgroups based on the CTCL subtype: MF and SS ($n = 97$, of which 89 MF and 8 SS) and other CTCLs ($n = 30$) (Table 1). The group of other CTCLs included patients that were diagnosed with primary cutaneous anaplastic large cell lymphoma ($n = 11$); primary cutaneous CD4+ small/medium T-cell lymphoma ($n = 7$); cutaneous lymphomas not otherwise specified ($n = 7$); primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma ($n = 2$); primary cutaneous peripheral T-cell lymphoma, unspecified ($n = 2$); cutaneous CD4+ pleomorphic T-cell lymphoma ($n = 1$). The median age at diagnosis was 67 years for both MF and SS patients and other CTCLs. The male to female ratio was 1.5:1 in all CTCLs, 1.6:1 in MF and SS and 1.3:1 in other CTCLs.

The completeness of CTCL registration

Among the 127 patients, 54 patients (43%) were recorded in the SLR. There was an indication of lower completeness of SLR registration among patients diagnosed with MF and SS (37/97, 38%) than other CTCLs (17/30, 57%) (p for difference = 0.073). The completeness of SLR registration was significantly higher for MF and SS diagnosed in advanced stages (IIB-IVB, 16/20, 80%) than in early stages (IA-IIA, 21/76, 28%) ($p < 0.001$). No significant differences were observed in completeness by sex or age groups (Table 1).

Registration rates by hospital and type of clinic

The completeness of the SLR registration was lower for patients treated at KUH (35/101, 36%) than for the patients treated at UUH (19/26, 73%). Among the registered patients, 24/54 (44%) were registered from a hematology clinic, 14/54 (26%) from a dermatology clinic, 12/54 (22%) from an oncology clinic, and 4/54 (7%) from a private/unspecified clinic (Supplementary Table 1).

The timeliness of CTCL registration

The dates of registration were available for 42/54 (78%) registered patients. Dates were not available for patients registered before year 2007 ($n = 10$). The median time between the diagnosis and SLR registration was 12.7 months (range: 1.2–166.8 months). Of the patients with available data, 9/42 (21%) were registered within 0–6 months, 13/42 (31%) within 7–13.0 months, 8/42 (19%) within 13–19.0 months and 12/42 (29%) 19 or more months after diagnosis (Supplementary Table 1).

Overall survival

The median OS was 8.8 years (range = 0.1–16.8) for all patients and 9.2 years (range = 0.1–16.8) for MF and SS patients (Figure 1). The median OS was 4.6 years (range = 0.1–13.3) in registered and 11.1 years (range = 1.4–16.8) in unregistered MF and SS patients. This difference was statistically significant both with the log-rank test ($p = 0.001$) and using multivariable Cox regression adjusted for stage and age (hazard ratio 2.11, 95% confidence interval 1.01–4.44; $p = 0.049$) (Figure 1, Supplementary Table 2). Patients with other CTCLs ($n = 30$/127) than MF and SS were excluded from the survival analysis since this group is highly heterogeneous and lacks an established staging system.

Discussion

In this study, we performed a comprehensive multi-center cohort analysis of OS among CTCL patients as well as the first investigation of completeness and timeliness of CTCL registration in Sweden. The median OS for MF and SS patients was relatively short, and the median age was high compared to international data. As for the SLR validation, we show low CTCL patient completeness relative to medical

Table 1. Characteristics of the cutaneous T-cell lymphoma (CTCL) patients overall and by registration in the Swedish Lymphoma Register.

	Overall sample *n* (col%)	MF and SS *n* (col%)	Other CTCLs *n* (col%)	Registered *n* (row%)	Unregistered *n* (row%)	*p* Value[a]
Total (row%)	127 (100)	97 (76)	30 (24)	54 (43)	73 (57)	
Age at diagnosis						0.327
21–40 years	7 (6)	5 (5)	2 (7)	2 (29)	5 (71)	
41–60 years	31 (24)	24 (25)	7 (23)	13 (42)	18 (58)	
61–80 years	65 (51)	50 (52)	15 (50)	25 (38)	40 (62)	
81–100 years	24 (19)	18 (19)	6 (20)	14 (58)	10 (42)	
Sex, *n* (%)						0.630
Male	76 (60)	59 (61)	17 (57)	31 (41)	45 (59)	
Female	51 (40)	38 (39)	13 (43)	23 (45)	28 (55)	
TNMB-stages[b,c]						<0.001
Stage IA–IIA	76 (60)	76 (78)		21 (28)	55 (72)	
Stage IIB–IVB	20 (16)	20 (21)		16 (80)	4 (20)	

Values were reported as numbers and column or row percentages (in parentheses).
MF: mycosis fungoides; SS: Sézary syndrome; CTCL: cutaneous T-cell lymphoma; TNMB: tumor-node-metastasis-blood.
[a]Chi-square test for registered vs. unregistered CTCL patients, $p < 0.05$ was considered statistically significant.
[b]The TNMB staging system is commonly used for MF and SS but not for other CTCL subtypes.
[c]Data were not available for one patient with MF.

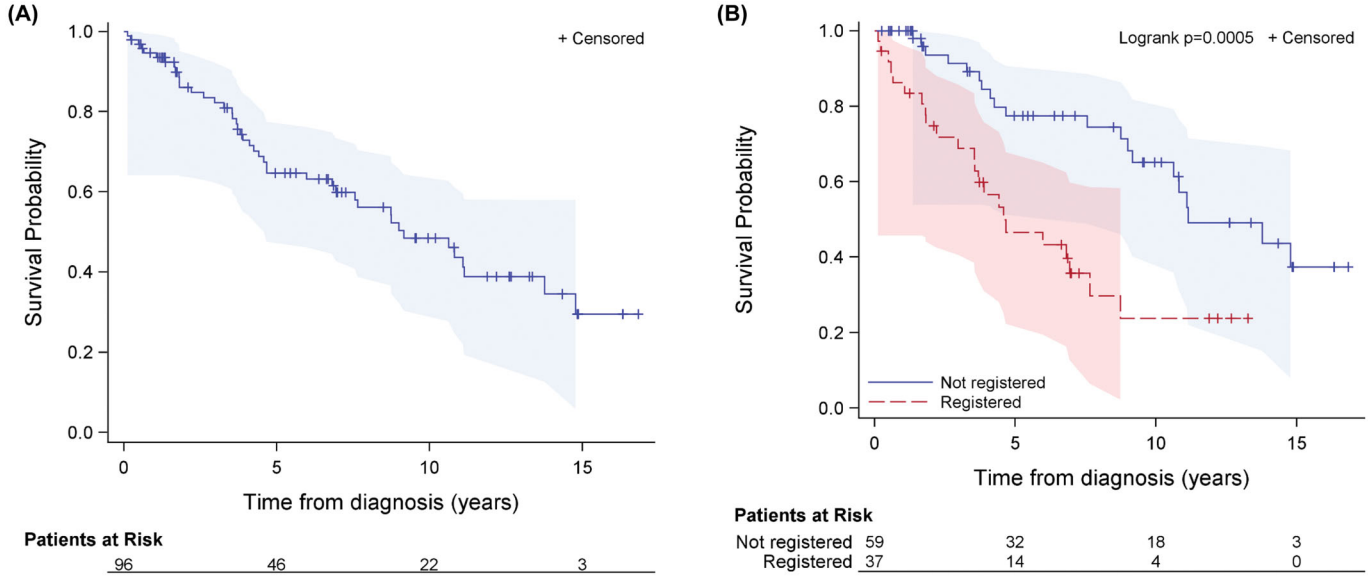

Figure 1. Kaplan–Meier estimates of overall survival for (A) all mycosis fungoides and Sézary syndrome patients and for (B) The Swedish Lymphoma Register-registered versus unregistered mycosis fungoides and Sézary syndrome patients. Date of diagnosis was not available for one patient.

records and long median time between diagnosis and registration. Patients with advanced-stage disease and poor OS were registered more often. These findings have important implications for future CTCL research based on registry data.

In the current study, the male-to-female ratio in MF and SS patients (1.6:1) was similar to previous Swedish and international data [7,13]. The median age at CTCL diagnosis was higher than previously reported in the UK (67 vs. 54 years) but similar to an earlier Swedish report (64 years) [7,13]. This study did not find any significant differences in underreporting between men and women or between different age groups. In contrast, non-reporting and low validity of overall cancer and lymphoma data has been associated with high age and female sex in previous studies [14–18].

The median OS for patients with MF and SS in our study was lower than the median OS reported in the UK (9.2 years vs 18.3 years) which might depend on the relatively high median age and low-risk for selection bias in our nearly population-based cohort compared to the single-center study [7]. In a recent population-based study the median OS for MF patients diagnosed in 1990–1999 was above 17 years and the median age was 62, whereas the median OS was not reached for patients diagnosed after 2000 [19]. The survival of patients with MF has improved between 1970 and 2000, which underscores the need for more recent studies on OS [11,19]. The heterogeneity of the group of other CTCL subtypes complicates the interpretation of OS in patients with non-MF and SS and the entire CTCL cohort.

The overall completeness of CTCL patient registration (43%) found in this study is far below the average completeness of the SLR for all lymphoma patients (>95% for years 2015-2016; >90% for 2017–2018; >75% for 2019-2020) [12]. One possible explanation for the low completeness is the indolent course CTCL takes in most patients. Our results show that the completeness of SLR registration was significantly higher for CTCL in the advanced stages IIB–IVB than CTCL in the early stages IA–IIA. Also, previous Nordic studies investigating the completeness of lymphoproliferative disorder registration, observed that underreporting was more common in indolent and early-stage disease [14,20].

Furthermore, OS was significantly worse for registered vs. unregistered MF and SS patients in univariate analysis. Multivariable cox regression analysis indicated that this difference was affected by different stage and age distributions within registered and unregistered groups, but the difference remained significant suggesting that patients with poor overall health and perhaps higher CTCL disease activity are registered more often.

As most CTCL patients do not progress to advanced stages [7], the majority are managed at dermatology clinics only. However, in our study population, the majority (67%) of the registrations had been made by oncological and hematological clinics. A possible explanation for this is that these clinics may have better-established routines for CTCL registration as they regularly report other lymphoma patients in the SLR. Also, the diagnosis of early-stage CTCL is often challenging and prolonged, which might decrease the registration rate from dermatology clinics [21].

Delayed reporting of CTCL patients to the SLR may explain part of the low completeness of CTCL registration. The analysis of the timeliness reveals that the median time from diagnosis to SLR registration of CTCL patients was 380 days, which is considerably longer than the corresponding time for all lymphoma patients registered in Stockholm and Gotland (190 days) [12].

Using medical records as a baseline for a registry validation study has its limitations due to the risk of inconsistent documentation of patient data in the hospital records. Having SCR as the gold standard was, however, not feasible since discrimination between CTCL and other lymphoma patients is not possible based on SCR data. Also, some patients diagnosed with CTCL in Stockholm and Uppsala counties may not have been included in the study as we only used medical records from the major university hospitals of these counties. We estimate, however, that the number of missing cases is low and that the study reaches nearly a population-based level as the treatment of CTCL is highly centered to specialized clinics in these counties.

Conclusion

This is a comprehensive multi-center cohort analysis of OS and patient characteristics among CTCL patients and the first study evaluating the data quality of the SLR regarding CTCLs. We found that the median OS for MF and SS patients was short, and the median age was high compared to international data. SLR had a low degree of completeness for CTCL patients. Furthermore, the latency time for a CTCL diagnosis to be reported in the SLR was long and the reporting was skewed toward patients with advanced-stage disease and poor survival, which poses challenges for data interpretation. This study underscores the importance of continued registration vigilance in Sweden as well as internationally.

Disclosure statement

HB has received honoraria from participating in advisory boards of Kyowa Kirin in 2019. KES has ongoing research collaboration with Janssen, outside the scope of this study. The other authors report no conflicts of interest.

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