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Epidemiology of cutaneous T-cell lymphomas: state of the art and a focus on the Italian Marche region

Among primary cutaneous T-cell lymphomas (CTCL), mycosis fungoides (MF) is the most frequent and, along with Sézary syndrome (SS), the best-studied subtype. Most available studies on epidemiology of MF and SS are based on small cohorts or different inclusion criteria. Moreover, although this has become a hot topic, most studies show limitations, such as selection bias and lack of clinical information or follow-up data. Therefore, no reliable conclusions can be drawn. This paper reviews the current data underpinning our understanding of the epidemiology of MF and SS, and presents some original findings based on data retrieved from the cutaneous lymphoma registry of the Italian Marche region. The Marche Regional Cutaneous Lymphoma Registry is a multidisciplinary team founded 27 years ago to share the management of these rare disorders. All patients with a clinical and histologically confirmed diagnosis of primary cutaneous lymphoma are centralized in Ancona (Italy) at the Haematology Clinic, Polytechnic University of Marche, for clinical evaluation, staging, treatment, and follow-up. This paper emphasizes the need for a national registry of pCLs in Italy, as no detailed epidemiological information is available in the country except for the Marche Regional Cutaneous Lymphoma Registry. A national registry would allow for more comprehensive data collection from all over Italy and could provide more accurate information on incidence and epidemiology. This would be beneficial for understanding the pathogenesis and diagnostic procedures of these diseases and could improve patient outcomes. Therefore, we advise the creation of a national registry of pCLs in Italy.

Keywords: cutaneous lymphomas, Italy, SS, MF, prevalence, epidemiology, statistics

Epidemiology of mycosis fungoides and Sézary syndrome

Primary cutaneous lymphomas (pCLs) are a heterogeneous group of non-Hodgkin lymphomas that primarily affect the skin with no sign of extranodal disease for at least six months following cutaneous presentation [1]. In contrast to nodal/systemic lymphomas, primary cutaneous forms predominantly have a T-cell phenotype [1]. Among primary cutaneous T-cell lymphomas (CTCL), mycosis fungoides (MF) is the most frequent and, along with Sézary syndrome (SS), the best studied subtype. Altogether, they account for around one half of CTCL diagnoses [2-4]. The prognosis for early-stage MF is not dissimilar to healthy controls, which generally pursues an indolent clinical course but disease progression may occur in a subset of patients, including extracutaneous spread. By contrast, SS is a much more aggressive subtype associated with a median survival of only around three years [5]. Currently, the pathogenetic mechanisms of MF and SS remain to be fully elucidated.

Diagnosis can be tricky, especially in the early stages of MF, where skin presentation (patches and plaques) may mimic benign dermatoses such as eczema or psoriasis, or in the case of SS, where the skin presentation may be attributed to more common causes of erythroderma, including drug reaction or atopic dermatitis. In early

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MF lesions, the histopathological features that differentiate MF from benign inflammatory diseases are still a debated and critical issue. Molecular biology may also reveal limited value in early MF because of the few lymphoma cells in the skin biopsy. Perhaps for this reason, and as recently observed by the PROCLIPI study [6], the median diagnostic delay for early-stage MF is 36 months, with the final MF diagnosis sometimes requiring prolonged follow-up and repeated biopsies. Only cases of allogeneic haematopoietic stem cell transplant have been shown to have responses that are sufficiently long to be considered as "curative", though this approach is only suitable for a very select group of patients. Skin-directed treatments are the mainstay for early-stage MF, with systemic treatments becoming more frequently used for refractory or advanced-stage cases.

Little is known about the epidemiology of MF and SS, and most of the available studies rely on small cohorts of patients or are based on different inclusion criteria [2-5, 7-18]. In the last few years, epidemiology has become a hot topic, and different studies have attempted to analyse MF/SS incidence in different geographic areas or [2, 4, 7-16, 18-2] countries. Most studies demonstrate that MF/SS affects men more than females, with a median age between 55 and 60 years [9, 10, 15, 16, 23], although there are contrasting results, especially in incidence trends. From 1998, most studies show a stable incidence in the USA (which had previously tripled from the 1970s) [2, 3, 5, 9, 10, 20], while a recent study hypothesizes that the incidence may be increasing in the USA on a par with European countries [4, 19, 21]. As assumed by Vermeer *et al.* [24], a possible bias of the epidemiological studies available may be due to the selection of the database. Indeed, most of the studies were based on tertiary referral centres or pathology registries. These tertiary referral centres may present limited and highly specific cohorts of patients, while registries based on pathology data may lack clinical information or follow-up information.

Furthermore, most US studies are based on Surveillance, Epidemiology, and End Results (SEER) databases. Such registries were not designed for malignant diseases in general and show some limitations due to the fact that clinical information is provided for about 50% of the US population. It seems reasonable that cases classified as CTCL but not further subtyped could be retained as "not otherwise classified". Thus, no reliable conclusions can be drawn for MF and SS epidemiology.

The present paper aims to review the current data underpinning our understanding of the epidemiology of MF and SS and present some original findings based on the epidemiological data retrieved from a single regional (Marche) cutaneous lymphoma registry.

Epidemiology in the US

Most of the studies present in the literature have been undertaken by US groups and are based on the SEER database. They show a historically increasing trend in MF/SS incidence since the 1970s [3, 5, 7-10]. However, a stable incidence estimated at 4.0 cases per million persons per year has been observed over the last decade [2, 3, 5, 9, 10, 20]. A possible explanation for the increased incidence between 1970 and 2000 may be due to the increased capacity for accurate and early diagnosis based on the development of immunohistochemistry and molecular biology analysis. Furthermore, the European Organisation for Research and Treatment of Cancer and the International Society for Cutaneous Lymphoma provided an algorithm for the diagnosis of early-stage MF in 2005 [25], a tool that has helped physicians to avoid under/over-estimating early diagnosis.

With regards to incidence, a recent paper by Cai *et al.* [21] revealed results diametrically opposed to those that have highlighted a stable incidence in the US. The authors analysed data from 18 population-based registries of the SEER between 2000 and 2018. A total of 14,942 new CTCL cases were identified (a larger cohort than that in previous studies) [3, 7, 8, 10, 22] in which MF was the most common diagnosis with an annual percentage change (APC) estimated at 5.42%, while SS showed a 3.83% APC. Non-Hispanic Black patients showed the highest incidence changes (APC, 11.68%) and male gender was most commonly affected (APC 10.68%). Such data follows the literature [2, 3, 5, 7, 8, 13-16, 20], and is consistent with an incidence rate six times higher in patients over 40 years of age. However, the study revealed that people below the age of 40 had a significantly higher increase in MF (APC, 3.67%) as well as women (APC, 0.92%), non-Hispanic Black patients (APC, 1.63%), patients in the lowest socioeconomic status (APC, 1.87%), and individuals in metropolitan areas (APC, 0.68%). As for the MF increase in young patients, the authors speculated whether the surge of new diagnoses could be related to earlier detection or the fact that the usage of biological agents may unmask cases previously misinterpreted as atopic dermatitis or psoriasis. The trend in an increase in MF and SS diagnosis was not confirmed recently by Kayishunge *et al.* [2] based on analysis of SEER and an in-house database of 143 patients, which represents a small cohort of patients.

Another interesting issue in the literature is related to the putative occurrence of clusters of higher incidence in the US, as reported by Litinov *et al.* [15] and Korgavkar *et al.* [26]. Korgavkar *et al.* [26] found that San Francisco had a much higher age-adjusted incidence rate in both 1992 and 2009 (incidence of 13.4 per million persons and 20.3 per million, respectively) than San Jose (incidence of 4.3 per million persons in 1992 and 9.7 per million in 2009). Recently, Malachowski *et al.* [20] observed similar findings based on analysis of the CTCL incidence in Florida, identifying Palm Beach County as a single region of higher incidence (7.91 per million), whereas close areas such as Miami-Dade, Santa Rosa, Seminole, and Leon counties showed significantly lower rates. Similar regional differences have also been observed in Canada and other US areas [2, 16].

In Brazil and South America, similar data were shown to those from North America. Miyashiro *et al.* [27, 28] analysed 727 Brazilian patients and observed a higher percentage of hypopigmented MF. Another interesting finding was that the median age of 51.8 years was slightly lower than that reported in the literature.

Epidemiology in the EU

There are fewer epidemiological studies in European Countries than in the US which mainly focus on MF/SS. A recent meta-analysis by Dobos *et al*. [4] highlighted that MF and SS are more frequent in Europe than in North America [29-44]. One of the pioneer studies on European CTCL epidemiology was carried out by Grange *et al*. [29]. The study focused on patients retrieved from the registry of the French Study Group on Cutaneous Lymphomas (FSGCL) from January 1st, 1986, to March 1st, 1997. One hundred and fifty-eight cases were collected, including 73 CTCLs. The study was mainly focused on searching for possible prognostic parameters, while from an epidemiological point of view, it corroborated the fact that PCLs primarily affect males in the sixth decade. Epidemiological data were provided later on, by Saunes *et al*. and Abbott *et al*. [39, 40]. The former group reported CTCL incidence in Norway, while the latter in Wales. The Norwegian study [39] analysed changes in CTCL incidence over 20 years (1980-2003), highlighting a significant increase in the incidence of MF/SS, rising from 0.15 per 100,000 persons/year to 0.18 per 100,000 persons/year. The study had a cohort of patients (337) larger than that of Abbot *et al*. (120 patients) [40], which might explain some differences between the data of Saunes *et al*. (crude incidence rate over 8.3 years of 0.48 per 100,000 persons/year and the age-adjusted incidence rate of 0.39 per 100,000 persons/year) and the data in the literature (7.7 per 100,000 persons/year reported by Bradford *et al.* [10]). Most recent studies have highlighted an increase in CTCL incidence also in Europe [4, 19, 45, 46]. Dobos *et al*. [4] analysed 8,593 patients collected by the French Cutaneous Lymphoma Registry. The French researchers reported epidemiological changes between 2005 and 2019, observing different trends over three different periods (2005-2009, 2010-2014, 2015-2019). A decrease in conventional MF incidence was found (50.2% of diagnoses between 2005 and 2009 reduced to 29.1% between 2015 and 2019). However, an increase in MF subtypes, such as folliculotropic MF (FMF), was observed (from 0.5% to 8.8% of the total diagnoses of CTCL between the above-mentioned periods). The improvement in diagnostic skills and techniques may account for such findings as well as the increase in CTCL subtypes other than MF/SS (such as small/medium-sized CD4+ lymphoproliferative disorder). Dobos *et al*. [47] registered an incidence of CTCL estimated at 0.96 per 100,000 persons/year, which was higher than what had been previously reported [39, 40].

A trend towards an increase in MF/SS incidence was reported by other groups, such as the Dutch group [19], which found a three-fold increase in MF and a six-fold increase in SS diagnosis over a 20-year period, as well as Keto *et al.* [46] who reported that MF and SS incidence varied from 2.04 to 5.38 and from 0.16 to 0.36 per 100,000 persons/year, respectively. The authors observed an increase in MF/SS diagnosis in individuals aged 0-29, a trend confirmed by a prospective Spanish study [45]. However, paediatric cases remain rare. Another Spanish study corroborated the increase in MF/SS annual incidence in the general adult population [4]. In Italy, no detailed data are available. The only extrapolated data is MF/SS incidence estimated at 6,800 cases (4,900 in early stage) [49]. The same group estimated Italian incidence at 270-330 new cases annually. However, the lack of an Italian lymphoma registry makes it difficult to extrapolate any epidemiological conclusions.

Epidemiology in Africa

Data in Africa are scarce and inconclusive. In a retrospective study by Erraji *et al*. [50], 166 patients in Casablanca were analysed between 1988 and 2018. The African researchers estimated an increase in MF/SS incidence (from 0.36 to 0.55 per 100,000 person-years) with 25% of patients under 40. However, the absence of more extensive studies makes it difficult to draw any conclusions.

Epidemiology in Australia/Asia

Epidemiological studies in Australia and Asia are scanty. Only two studies in Asia reported global epidemiological data albeit none of them analysed incidence rates. Hence, it is impossible to draw a conclusion on CTCL incidence over time in Asian countries [51, 52]. Recently, Lim *et al*. [53], by analysing Singapore Hospital data, observed that in South-East Asia, MF/SS was diagnosed in younger individuals and was associated with a lower level of mortality and a greater prevalence of hypopigmented MF than expected. In Australia, MF/SS incidence has been estimated at 0.15 per 100,000 people/year [10, 54]. A recent study, focused on the New Zealand area and especially on Māori/Pacific people, found that the incidence of MF/SS in these ethnic groups was not high, while New Zealand incidence was estimated at 0.37 per 100,000 persons/year, thus corroborating the data in the literature.

Regional registry of the Marche region

Introduction

No exhaustive epidemiological data are available in Italy except for the Marche Regional Cutaneous Lymphoma Registry. The Marche region is geographically set in central Italy, with a population of about 1.5 million people (2.5% of the Italian population). Twenty-seven years ago, a multidisciplinary team (MDT) for diagnosis and follow-up of cutaneous lymphomas was set up to share the management of these rare disorders. All patients with a clinical and histologically confirmed diagnosis of primary cutaneous lymphoma were centralized by participants of the MDT to the Clinic of Haematology, Polytechnic University of Marche in Ancona (Italy), for clinical evaluation, staging, treatment, and follow-up.

One of the main goals of the MDT was to register the number and types of cutaneous lymphomas across Marche to estimate the incidence, survival rates, and other outcome data. With the aid of all the members of

the MDT, the cases are still registered anonymously and dynamically with follow-up reporting. All dermatology and haematology units across Marche are invited to communicate the data of patients with cutaneous lymphomas to the central registry to promote comprehensive reporting.

Methods

In the event of first diagnosis, a "first report" is sent to the registry, including age, gender, occupation, exposure to toxins, concomitant diseases, haematological/oncological disease, previous radiotherapy, previous chemotherapy, severity of skin lesions (macules, plaques, tumours, ulceration, erythroderma, percentage of involved body surface), time from first skin lesion to diagnosis, histology, location, lactate dehydrogenase level, flow cytometry data, molecular biology (clonality), bone marrow data, and stage. For staging of MF/SS, the TNMB classification according to modified ISCL/EORTC 2011 revision is employed [55]. In follow-up reports, additional detailed information regarding treatment and/or change of stage (stage, transformation) is recorded. In several cases, patients received their initial diagnosis from an MDT member and were referred to the Ancona Haematology Unit for further evaluation and management. Most patients' slides have been reviewed by an experienced dermato-haemato/pathologist to confirm the diagnosis. Throughout the observation period mentioned, reports have continually increased, probably mainly due to enhanced reporting activity, the number of centres reporting, and attention to this pathology (*figure 1*). The study was approved by the human research ethics committee of "AOU delle Marche" Hospital, and prior written informed consent was obtained from all the participants. Demographic characteristics and age groups were assessed and reported (*table 1*). Patient characteristics were summarized by frequency (percentage) for categorical variables and median (range) values for continuous variables. Overall survival (OS) was defined as the time from diagnosis until death from any cause. Survival data were evaluated by the Kaplan-Meier method with differences between groups compared by log-rank test. Statistical analysis was performed using JMP 14.0, and significance was defined as $p<0.05$.

Results

Clinical features

During the study period 1995–2020, 628 patients with newly diagnosed cutaneous lymphomas were reported and evaluated. Among these, CTCL cases were predominant (492 patients, 78.3%), while primary cutaneous B-cell lymphomas (CBCL) comprised 21.7%, thus corroborating the data in the literature. Median age at diagnosis was 62 years (range: 10-90), while different diagnoses were related to different peaks of incidence. Indeed, median age of patients with MF was 63 years (range: 19-90), while patients with lymphomatoid papulosis had a median age of 49 years (range: 10-77). CTCL showed a higher prevalence in men than in women (M:F = 2.3:1). Details of clinical characteristics, primary site of presentation and summary stage at diagnosis are reported in *table 1*.

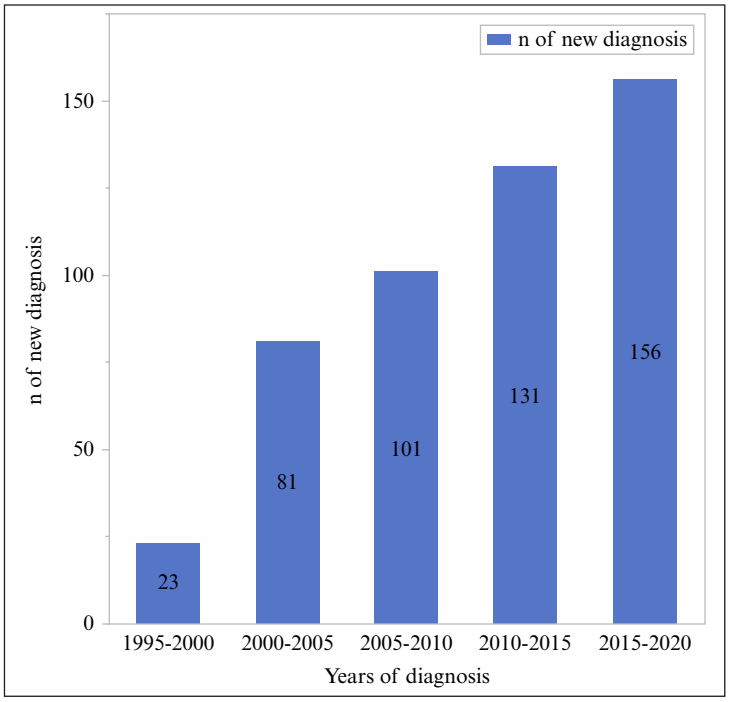

Figure 1. Registration of the MDT Registry (1995-2020).

Table 1. Clinical characteristics, primary presentation site and summary stage at diagnosis among 492 CTCL patients.

Characteristic	*N* total= 492
Sex	
M	316 (64.2)
F	136 (35.8)
Age	
<50	123 (25)
50-59	87 (17.7)
60-69	140 (28.5)
70-79	88 (17.9)
>80	54 (11.1)
Skin lesion at diagnosis*	
Patches	340 (69.1)
Plaques/ Papule	75 (15.4)
Tumours	42 (8.5)
Erythroderma	35 (7.1)
Primary site	
Skin of extremities	299 (60.7)
Skin of trunk	286 (58.1)
Skin of the head and face	61 (12.3)

CTCL: primary cutaneous T-cell lymphomas.
**According to the current classification, patients presenting with cutaneous lesions at different stages are classified under the most advanced stage.*

Table 2. Histological features according 2018 WHO/EORTC classification among 492 CTCL patients.

WHO-EORTC 2018 classification	Number, (frequency %)
Mycosis fungoides	360 (73.2)
MF variant	26 (5.3)
Follicular MF	24 (4.9)
Pagetoid reticulosis	2 (0.4)
Sézary syndrome	25 (5.1)
Adult T-cell leukaemia/lymphoma	2 (0.4)
Primary cutaneous CD30+ LPDs	41 (8.3)
C-ALCL	7 (1.4)
Lymphomatoid papulosis	34 (6.9)
Subcutaneous panniculitis-like lymphoma	3 (0.6)
PCTCL, rare subtype	
Primary cutaneous γ/δ T cell lymphoma	1 (0.2)
CD8+ AECTCL (provisional)	5 (1)
Primary cutaneous CD4+ small/medium T cell lymphoproliferative disorder (provisional)	17 (3.4)
Acral CD8+	1 (0.2)
Primary cutaneous T cell lymphoma, NOS	11 (2.2)

AECTCL: aggressive epidermotropic cytotoxic T-cell lymphoma; C-ALCL: cutaneous anaplastic large cell lymphoma; CTCL: cutaneous T-cell lymphomas; LPDs: lymphoproliferative disorders; MF: mycosis fungoides; PCTCL: primary cutaneous T-cell lymphomas.

Table 3. Clinical characteristics and outcome data in 411 MF/SS patients, including cases with the MF variant.

Characteristic	*N* total= 411
Stage *n* (%)	
Ia	164 (39.9)
Ib	147 (35.8)
IIa	28 (6.8)
IIb	14 (3.4)
IIIa	15 (3.6)
IIIb	8 (1.9)
IVa	29 (7.1)
IVb	6 (1.5)
Median diagnostic delay, months (range)	21 (0-562.9)
Early stage	22.1 (0-562.9)
Advanced stage	7.8 (0-46.9)
Median follow-up, months (range)	67 (5.7-308.6)
5-year survival rate	86.7%
Early stage	94.2%
Advanced stage	48.7%

MF: mycosis fungoides; SS: Sézary syndrome.

Pathological features

Historically, MF and its variants were the most common registered cases (77.5%), followed by CD30+ cutaneous lymphoproliferative disorders (8.3%) and SS (5.1%). Among rare T-cell lymphomas, primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder encompassed 3.4% of cases, while primary cutaneous peripheral T-cell lymphoma not otherwise specified corresponded to 2.2% of all the evaluated cases (*table 2*). As previously mentioned, most patients had a diagnosis of MF/SS and more than 80% had early-stage disease (IA, IB and IIA; *for details see table 3*). Bone marrow evaluation was carried out in 38.4% of cases. Thirty-eight patients showed a circulating clone and TCR rearrangement was demonstrated in 23.8% of patients by RT-PCR from peripheral blood samples. In all cases, the presence of neoplastic cells in the peripheral blood was evaluated in order to rule out any under-staging of the patients. Using flow cytometry, blood involvement was found in 48 patients (7.6%), and B2 was detected in 1.1% of total cases of MF, according to ISCL/EORTC revised classification.

Treatment considerations and survival data

Concerning the diagnostic delay, median time from first skin lesion to diagnosis was 21 months (range: 0-562.9); longer for early-phase disease than advanced-stage (22.1 months vs 7.8 months, respectively; p=0.04), a finding in line with the PROCLIPI study [6]. Concerning scheduled treatments among skin directed therapies (*for further details, see figure 2*), phototherapy was largely used in 42.6% of cases, both as a monotherapy or combination treatment. Among immunomodulatory agents, bexarotene, methotrexate or interferon (available at the time the registry was established) were used as first-line therapy in 135 patients (28.8%). With a median follow-up of 67 months (range: 5.7-308.6), the combined five-year survival rate was 86.73%; less favourable for advanced stages compared to early stages (48.7% and 94.2%, respectively; p<0.001) (*figure 3*).

Final consideration

In conclusion, our analysis of the data from a small region in Italy highlights the increasing incidence of cutaneous lymphoma diagnoses, potentially attributed to improved diagnostic techniques and centralized treatment options.

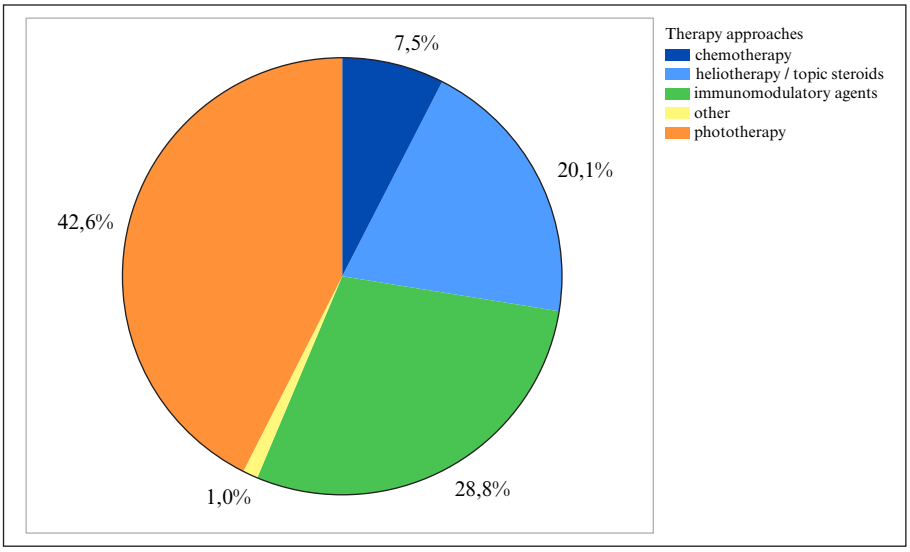

Figure 2. First-line therapy approaches among MF/SS patients.

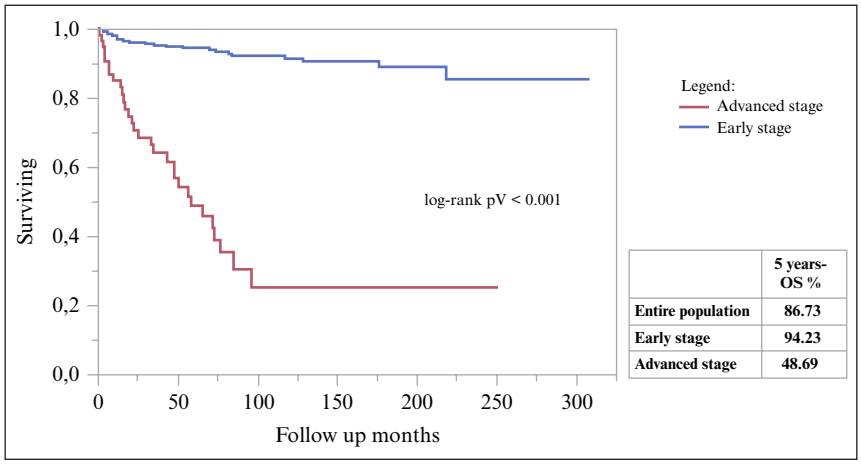

Figure 3. Overall survival in 411 MF/SS patients, according to early and advanced stage.

This incidence rate may be underestimated, especially in the early years of observation, due to the lower number of patients referred to the coordinating centre. Furthermore, it emphasizes the importance of accurate staging for determining patient prognosis. These findings align with existing literature and lay the groundwork for further research, particularly through ongoing studies, such as PROCLIPI, to better understand the impact of novel therapies on patient outcomes.

Discussion

The actual epidemiology of pCLs is still being debated and can be considered a "hot topic". As previously mentioned, it is essential to acknowledge certain limitations and challenges faced by researchers in this field. Epidemiological studies on pCLs have encountered a variety of inclusion criteria that have evolved over the years due to changes in diagnostic criteria and available treatment options. In most, analysed registries were missing clinical-pathological correlations, and different classification systems were used without a comparable recruitment period.

Future studies on pCLs epidemiology should use a prospective design to include data on survival. Information is also needed on the staging of lymphomas, including the non-MF/SS types. The inclusion of treatments and outcomes in such registries would help achieve progress in patient care. In fact, the current staging system for pCLs is an important tool for assessing disease progression and guiding treatment decisions. However, its ability to accurately reflect the survival outcomes of patients, especially in the context of modern treatments, can be a subject of discussion.

Hence, our current knowledge is still too far from allowing us to draw any reliable conclusions on epidemiology. The discrepancy in database selection represents an important bias. The SEER database can encompass a high number of patients but can only show a picture of approximately 50% of the US population. Tertiary

referral centres enrol smaller cohorts of highly selected patients (a condition for biased selection). To date, in Italy, epidemiology is still far from being elucidated. The only available appraisal has been provided by an expert consensus report, which has estimated MF/SS prevalence in 6,800 cases, 75% of them in the early phase [48]. Unfortunately, no national data are available for either non-MF/SS CTCLs or for CBCLs. Currently, international studies with a central clinico-histological review of cases, such as that initiated by the Cutaneous Lymphoma International Consortium (PROCLIPI), are extremely valuable in allowing a prospective analysis of pCL frequency, outcome, and prognostic factors worldwide. PROCLIPI represents a formidable effort to gather data and tissues on early MF from multinational expert centres and should in the coming years yield a wealth of answers including information on patient management, as well as the risks of progression to more aggressive stages of CTCL. Some potential enhancements to this data collection effort would be to include rarer histotypes, involving more centres. These steps would address the existing data gaps for these less common subtypes and help guide dedicated therapeutic approaches. In addition to such international projects, prospective national registries are urgently needed.

As previously shown, the only available data on pCLs in Italy is local, related to just one region of central Italy (Marche). The creation of such a database resulted in a collaborative effort to consolidate all the cases of pCLs observed in the Marche region. It serves as an example of cooperation between various dermatological and haematological units within the region. As stated above, the Marche registry data substantially corroborates with that of the literature. However, no clear-cut epidemiological analysis of the entire country can be drawn based on data from one region.

For this reason, the aim of the Italian Cutaneous Lymphoma Study Group (ICLSG-named Commissione Linfomi Cutanei) is to extend the Marche model to the national level by creating a national registry for pCLs. By means of prospective data collection, ICLSG can provide an accurate "picture" on pCL epidemiology in Italy and assess whether clusters with high/low incidence can be identified. ■

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Data availability statement: *the data supporting this study's findings are available upon request from the corresponding author.*

Ethics statement: *the study was conducted according to the principles of the Declaration of Helsinki.*

Patient privacy: *the patients in this manuscript provided written informed consent for the publication of their case details.*

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