Epidemiology of Cutaneous T-Cell Lymphomas: A Systematic Review and Meta-Analysis of 16,953 Patients

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Simple Summary: Cutaneous T-cell lymphomas (CTCL) are rare malignant diseases. In this study we have compared the cutaneous lymphoma registries of different countries, which included information on at least 100 patients. The frequencies of each CTCL subtype were compared within and between continents. We found that the registries differed importantly in terms of size and quality. Some rare CTCL subtypes, such as NK/T-cell lymphoma or subcutaneous panniculitis-like lymphomas, were more frequent in Asian countries, while others were evenly distributed. We discuss possible reasons for this and provide suggestions on how to build future CTCL registries.

Abstract: Cutaneous T-cell lymphomas (CTCL) are a heterogenous group of rare diseases. Many studies have reported on local epidemiology or geographic clustering, however we lack information from a global perspective. A systematic review and meta-analysis was conducted in Medline and the Cochrane Library based on a previously registered protocol and according to the preferred reporting of items for systematic reviews and meta-analyses (PRISMA). We selected publications that enrolled at least 100 patients with primary cutaneous lymphomas according to the current classifications. The relative frequencies (proportions) of subtypes were compared between studies and geographic regions in a meta-analysis. In total, 26 studies met our inclusion criteria, reporting on altogether 16,953 patients. Within primary cutaneous lymphomas, CTCL appeared to be 15% more frequent in Asian populations. Mycosis fungoides (MF) accounted for 62% of CTCL, with an important heterogeneity in frequencies between studies and continents. The proportion of Sézary syndrome (SS) was 3%, stable worldwide. Rare CTCL, such as NK/T-cell lymphoma or subcutaneous panniculitis-like lymphoma, were more frequent in Asian studies. This global meta-analysis of CTCL confirmed the predominance of CTCL among primary cutaneous lymphomas (83% on average) in the three analyzed continents, most of which were MF cases. It revealed the same proportions of SS across continents, and the heterogeneity of MF frequencies, suggesting the possible role of environmental factors in the pathophysiology of the latter. Registration number: CRD42020148295 (PROSPERO).
Keywords: cutaneous T-cell lymphomas; lymphomas; skin; mycosis fungoides; systematic review

1. Introduction

Primary cutaneous lymphomas (CLs) are a heterogenous group of diseases belonging to the extranodal non-Hodgkin lymphomas. Contrarily to their systemic counterparts, primary cutaneous T-cell lymphomas (CTCL) are more frequent than primary cutaneous B-cell lymphomas [1].

The pathogenesis of CTCL is not fully understood. Clustering CTCL patients have been reported in multiple areas worldwide, including in Sweden [2], Canada [3], Pennsylvania [4] and Texas [5], suggesting a potential environmental exposure. The skin is a barrier organ, and various exposures, including ultraviolet radiation, were described to play a role in the occurrence of malignancies. A mutational profile consistent with ultraviolet B exposure has been identified in CTCL [6], but a causal role of ultraviolet exposure in the occurrence of CTCL has not yet been demonstrated. Several epidemiological studies have been reported [7–16], but no worldwide meta-analysis has been published to date.

The aim of this study was to describe the epidemiology of CTCL from a global perspective by a systematic review of the literature and meta-analysis. We also aimed to compare the cohorts based on geographic regions to identify a potential spatial clustering of cases, and to analyze the variations of the frequencies of different subgroups of CTCL over time.

2. Results

2.1. Study Characteristics

Altogether, 256 publications were identified in the database search, and an additional 3496 records were found in the references of the full-text studies. After the removal of duplicates, 501 articles remained, of which 92 met the inclusion criteria and were read in full. Of these, 26 were included in the meta-analysis. The most frequent reasons for study exclusion were the enrolment of less than 100 patients (1) or the reporting of less than three subtypes of cutaneous lymphomas (2) (detailed in Figure 1). A list of excluded studies is shown in the Table S2, with reasons of exclusion.

The characteristics of included studies are displayed in Table 1 and Figure S1. In total, 16,953 patients from 26 different studies were enrolled in the present meta-analysis. The majority of the studies were reported in European populations; only one South American cohort [7] met the inclusion criteria, and none from Australia or Africa did. The publication dates were evenly distributed over two decades, however there was a gap between 2014 and 2018. The number of included subjects ranged from 120 [11] to 4310 [10]. The study periods varied between four years and decades, and were not precise in two studies [17,18]. Eight reports were considered representative by the authors [10,19–25]. Many studies from the USA used data from local cancer surveillance registries [10,19–21]. The majority of the studies had a prospective inclusion of patients and were multicentric. Only three of them stated a consecutive inclusion of patients. Out of 26 publications, 15 used the World Health Organization-European Organization for Research and Treatment of Cancer (WHO-EORTC) classification; 3 used the WHO [11,19,21] and 3 the EORTC [8,26,27] system, and 3 used a combination of these [8,14,28,29]. In two publications the used classification was not clearly defined [22,30]. Senff et al. [13] reclassified patients using the WHO, EORTC and the WHO-EORTC systems. In total, 15 articles reported the survival of the patients. Grange et al. [26] excluded mycosis fungoides (MF), Sézary syndrome (SS) and lymphomatoid papulosis (LyP) from their report, four studies included CTCL only [21–23,29] and three studies reported on CBCL only [13,15,19]. Six publications presented a reporting bias and eight a classification bias.
Here we report on CTCL only, because there were only minor changes in CTCL between the classification systems. This allowed us to perform a clustering analysis by continents. In total, 83% (95% confidence interval (CI), 70% to 86%) of the primary cutaneous lymphomas were CTCL, which was slightly lower in the European studies and higher in Asian and South American reports (Figure 2). The overall distribution of the CTCL groups varied considerably between the geographic regions (Figure 2).

**Figure 1.** Flowchart of study selection according to the preferred reporting of items for systematic reviews and meta-analyses (PRISMA).

**Figure 2.** Meta-analysis of the proportion of CTCL compared to all primary cutaneous lymphomas and overview of the subgroups.
Table 1. Characteristics of included studies.

| First Author | Year | Country | Inclusion of Patients | N   | Prospective Data Collection | Multi-Centric | Consecutive | Classification Used | Survival Reported | Reporting Bias | Classifi-Cation Bias |
|--------------|------|---------|-----------------------|-----|------------------------------|---------------|-------------|---------------------|------------------|----------------|----------------------|
| Grange [26]  | 1999 | France  | 1986–1997             | 158 | A                            | 1             | 1           | EORTC 1997          | 1                | 1              |                     |
| Zackheim [27]|
| 2000         | USA  |         | 1995–1998             | 755 |                              | 1             | 1           | EORTC 1997          | 1                | 1              |                     |
| Fink-Puches [28]|
| 2002         | Austria |   | 1960–1999             | 556 |                              |               |             | EORTC 1997 + WHO    | 1                |                |                     |
| Tan [14]     | 2003 | Singapore | 1990–2001            | 181 |                              |               |             | EORTC 1997 + WHO    | 1                |                |                     |
| Willemze [29]|
| 2003         | Netherlands | | 1985–1999             | 724 | B                            | 1             | 1           | WHO-EORTC 2005      | 1                | 1              | 1                   |
| Does [10]    | 2005 | USA     | 1992–2002             | 4310| C                            | 1             | 1           | WHO-EORTC 2005      | 1                | 1              | 1                   |
| Smith [19]   | 2005 | USA     | 1973–2001             | 4551| C                            | 1             | 1           | WHO-EORTC 2005      | 1                | 1              | 1                   |
| Willems [30] | 2005 | Austria + Netherlands | 1986–2002             | 1905|                             | 1             | 1           | WHO-EORTC 2005      | 1                |                |                     |
| Bouaziz [9]  | 2006 | France  | 1997–2003             | 203 |                              | 1             |             | WHO-EORTC 2005      | 1                |                |                     |
| Zinzani [15] | 2006 | Italy   | 1980–2003             | 467 | B                            | 1             | 1           | WHO-EORTC 2005      | 1                |                |                     |
| Assaf [8]    | 2007 | Germany | 1999–2007            | 998 |                              | 1             | 1           | WHO-EORTC 2005      | 1                |                |                     |
| Senff [13]   | 2007 | Netherlands | 1985–2005            | 300 | B                            | 1             |             | WHO-EORTC 2005      | 1                |                |                     |
| Bradford [20]|
| 2009         | USA  |         | 2001–2005             | 3845| C                            | 1             | 1           | WHO-EORTC 2005      | 1                | 1              | 1                   |
| Saunes [32]  | 2009 | Norway  | 1980–2003             | 325 | CD                           | 1             |             | not available       | 1                |                |                     |
| Doshi [30]   | 2011 | India   | 2004–2008             | 141 |                              |               |             | WHO-EORTC 2005      | 1                |                |                     |
| Fujita [11]  | 2011 | Japan   | 1995–2008             | 120 |                              |               |             | WHO-EORTC 2005      | 1                |                |                     |
| Hallermann [32]|
| 2011         | Germany | | 1980–2005             | 299 |                              |               |             | WHO-EORTC 2005      | 1                |                |                     |
| Jenni [12]   | 2011 | Switzerland | 1990–2009           | 263 |                              |               |             | WHO-EORTC 2005      | 1                |                |                     |
| Abbott [23]  | 2013 | United Kingdom | 2003–2011            | 120 | CD                           | 1             | 1           | WHO-EORTC 2005      | 1                |                |                     |
| Imam [21]    | 2013 | USA     | 2005–2008             | 2273| CD                           | 1             | 1           | WHO-EORTC 2005      | 1                |                |                     |
| Hamada [24]  | 2014 | Japan   | 2007–2011             | 1485| C                            | 1             | 1           | WHO-EORTC 2005      | 1                |                |                     |
| Han [25]     | 2014 | South-Korea | 2006–2010           | 321 | C                            | 1             |             | WHO-EORTC 2005      | 1                |                |                     |
| Maurelli [16]|
| 2018         | Italy |         | 2005–2015             | 141 |                              |               |             | WHO-EORTC 2005      | 1                |                |                     |
| Nashan [17]  | 2018 | Germany | 2005–2011             | 163 |                              | 1             | 1           | WHO-EORTC 2005      | 1                |                |                     |
| Penate [18]  | 2018 | Spain   | nk–2017               | 639 |                              | 1             | 1           | WHO-EORTC 2005      | 1                |                |                     |
| Abeldano [7] | 2019 | Argentina | 2010–2015            | 415 |                              | 1             | 1           | WHO-EORTC 2005      | 1                |                |                     |

nk: not known; A not reporting MF+LyP; B only reporting cutaneous B-cell lymphoma (CBCL); C considered exhaustive by the authors; D only cutaneous T-cell lymphoma (CTCL); EORTC 1997: European Organisation for Research and Treatment of Cancer 1997 classification [33]; EORTC 1997 + WHO: EORTC 1997 classification completed with elements of the World Health Organisation classification [34]; WHO: World Health Organisation classification [34]; WHO-EORTC 2005: WHO-EORTC 2005 classification [10].
2.2. CTCL Subtypes

2.2.1. Mycosis Fungoides and Sézary Syndrome

MF and SS represented 70% (95% CI 65% to 75%) of the CTCL and seemed to be less frequent in North America (65% (95% CI 55% to 75%)) than in Europe (73% (95% CI 67% to 78%)). The proportion of MF-SS compared to CTCL ranged from 40% (95% CI 34% to 46%) in South Korea [25] to 92% (95% CI 86% to 95%) in Singapore [14], with an important heterogeneity between the studies (Figure S2). Grouping the populations by continent could only explain 1% of this heterogeneity, and even within the continents the studies differed significantly. The same tendency could be observed when focusing only on MF, however here the heterogeneity within the North American studies was lower. The relative frequencies of SS varied between 1% (95% CI 1% to 2%) [21] and 15% (95% CI 10–21%) [12], in the USA and in Switzerland, respectively (Figure 3). Here, more homogeneity could be observed within the continents, and also between them. Grouping by regions could reduce the heterogeneity between the studies by 13%. In summary, MF was the most frequent CTCL, but the MF frequencies varied between the investigated cohorts, and this variation could not be explained by geographical differences. In contrast, the relative frequencies of SS seemed to be globally stable at 3% (95% CI 2% to 4%), and slightly more frequent in Europe. The distribution of MF variants is shown in Figure S3.

![Figure 3. Meta-analyses of the proportion of mycosis fungoides (MF) and Sézary syndrome (SS) compared to CTCL.](image)

2.2.2. CD30-Positive Lymphoproliferative Disorders

CD30-positive LPDs represented 16% (95% CI 13% to 19%) of CTCL, with the lowest in South America at 11% (95% CI 5% to 11%) and the highest in Europe at 19% (95% CI 14% to 24%).

The relative frequency of CD30-positive LPDs varied between 6% (95% CI 5% to 7%) [10] and 40% (95% CI 33% to 48%) [32] in the USA and Germany, respectively (Figure 4 and Figure S2). The heterogeneity between the studies was the lowest in Asia, this being 15% (95% CI 11% to 21%). The proportions were more homogeneous for ALCL, at around 7% (95% CI 5% to 9%). The relative frequency of LyP was 9% (95% CI 7% to 12%), with a similar pattern.
2.2.3. Rare Cutaneous T-Cell Lymphomas

The relative frequency of rare cutaneous T-cell lymphomas was 6% (95% CI 4% to 10%) and varied between 1% (95% CI 1% to 2%) [20] and 9% (95% CI 8% to 11%) [31] with the exception of Japan [11,24] and South Korea [25] (Figure 5 and Figure S2). Here, the relative frequencies were 27% (95% CI 19% to 37%) [11] and 39% (95% CI 33% to 45%) [25], respectively. Within the rare CTCL, subcutaneous panniculitis-like lymphoma, NK/T-cell lymphoma (Figure 5) and primary cutaneous T-cell lymphoma not otherwise specified (Figure S4) were more frequent in Asia. Adult T-cell lymphoma and leukemia (ATLL) were not included in the rare cutaneous lymphomas as a group, and were also more frequent in the reports from the Far East (Figure S2). On the other side, other rare lymphomas, including aggressive epidermotropic CD8-positive T-cell lymphoma, primary cutaneous Gamma-Delta T-cell lymphoma and small-medium cell CD4-positive T-cell lymphoma seemed to have similar frequencies around the world. Both within the continents and between the studies, the heterogeneity was importantly lower for each of these latter rare CTCL than for the frequent ones (Figure 5 and Figure S4).

Figure 4. Meta-analyses of the proportions of CD30+ lymphoproliferative disorder subtypes, primary cutaneous anaplastic large cell lymphoma (ALCL) and lymphomatoid papulosis (LyP) compared to CTCL.

Figure 5. Meta-analyses of the proportion of rare CTCL, subcutaneous panniculitis-like T-cell lymphoma (SPCTL) and NK/T-cell lymphoma compared to CTCL.
3. Discussion

In this systematic review and meta-analysis, we reported on the relative frequencies of each CTCL subtype as compared to the total of CTCL cases. We compared these between studies and within continents. A major finding was that CTCL within cutaneous lymphomas seemed to be 15% to 17% more frequent in Asian and South American countries as compared to Europe.

An overall improvement in reporting quality over time could be observed among the studies. From our point of view, it is important to report the time and place of patient recruitment, the use of the current classification system, and to mention if the inclusion is consecutive. Multicentric studies with prospective data collection should be preferred. Although many publications reported on the survival of CTCL patients, a recent systematic review [35] also pointed out the need for new data.

Information on the incidence of CTCL could be derived from some of the studies. Based on selected states, in the USA the incidence was estimated to be 0.77–0.87/100,000 person-years [10,20], whereas others reported an incidence of 0.64/100,000 person-years [36]. In Europe, the incidence was estimated to be 0.29–0.39/100,000 person-years [22,23], with a possible increase over time. In Asia, two studies [24,25] claimed exhaustive records, however none of them reported incidence rates. Due to the heterogeneity of the studies, it was not possible to draw conclusions on CTCL incidence over time. It was estimated in northern American works that the frequency of CTCL increased [37], while Korgavkar et al. [38] suggested a stabilization after this increase in 2013 in the same population. We believe that CTCL are still underdiagnosed, and thereby their number is probably underestimated [39].

The group of MF and SS, representing 70% of the CTCL, revealed an important heterogeneity between and also within the continents. Their lower frequency in North American studies may be explained by the study design in terms of the used registry. Earlier studies did not distinguish between MF and SS [27]; in this case, a separated evaluation of these diseases was not possible in our meta-analysis. It has to be emphasized that the majority of the American data were derived from the Surveillance, Epidemiology, End Results (SEER) program [10,20,21]. The registry used in these publications was not designed explicitly for cutaneous lymphomas, but for malignant diseases in general. Here, cases with uncertain classifications of CTCL subtype may be classed as “other”, including some early MF cases or rare CTCL, explaining the low numbers of MF cases and high numbers of NOS cases. In Asian countries, the proportion of rare CTCL was higher, affecting the MF/SS proportions. While SS represented everywhere 3% of CTCL, the relative frequency of MF was heterogenous. This suggests the influence of environmental factors in the pathogenesis of the latter. The geographical clustering of MF cases, and the occurrence of MF in married couples and families, has been reported in other studies [5], and raises the possibility of an environmental trigger for this malignancy. Lifestyle factors, or industrial exposures [3], may contribute to the pathogenesis of the disease. UV exposure has also been suspected to play a role in the disease pathophysiology [40]. A recent study suggested the role of environmental toxic exposures to benzene and trichloroethylene in the pathogenesis of cutaneous lymphomas [41].

CD30-positive LPDs, especially ALCL, showed less heterogeneity among the studies and continents. Similarly to SS, an innate predisposition of the lymphocytes may explain the occurrence of these diseases, independently from other factors.

Many rare cutaneous lymphomas appeared to be more frequent in Asia, and this was not only true for ATLL, a lymphoma associated with human T-lymphotropic virus (HTLV)-1 infection, which is endemic in Asia. It was proposed that ATLL is similarly frequent in Brazil as compared to Asia [42]. Unfortunately, only one study from South America met our inclusion criteria, while we identified a few reports on lower numbers of patients from Brazil [42,43]. Of note, MF/SS were the most frequent lymphomas, and the CD30-positive LPDs were 11% and 8%, respectively. At the same time, the ATLL accounted for 6% and 22% of CTCL, respectively, in these two excluded Brazilian reports, similarly to the Asian countries. The lowest heterogeneity between studies was observed for Epstein–Barr virus (EBV)-associated NK/T-cell lymphoma and SPTCL, even if these were more frequent in Japan and South Korea. Lymphoma-associated viruses are known to have a higher prevalence in Asia [11,42].
and probably in South America. SPTCL has been associated with the presence of germline HAVCR2 mutations, which are more frequent in Asian patients than in European ones [44]. For other rare CTCL, no geographic clustering could be identified in this study.

No publication from China or Africa could be included in this analysis, and some reports from South America and the Near East were excluded. The identified registries from China [45], India [46], Iran [47] or Israel [48] included around 60 patients, and many of them included less than 40 patients, so the comparison of their results is difficult. However, these data would have been interesting, since important differences in CTCL behavior were suggested in pigmented skin [20,49,50]. An additional confounder may be the use of different classification systems. For example, in some publications we were not able to extract the number of SS cases, since they were reported as MF-SS. The histological diagnosis of early MF is difficult, and these cases may have been handled differently between the included studies. There were slight changes between the CTCL classification systems, e.g., the primary cutaneous gamma-delta T-cell lymphoma was previously regarded as SPTCL. ATLL is not included in the EORTC [33] classification, and therefore a minority of the included studies may not have reported it (Figure S1). It is difficult to draw conclusions on trends in CTCL epidemiology over time, since no study reported on CTCL cases within the same geographical area at different timepoints without overlapping, as displayed in Figure S1. Finally, the definition of some lymphomas, such as the primary cutaneous T-cell lymphoma not otherwise specified (PTCL-NOS), has undergone refinement over time. The primary cutaneous gamma-delta T-cell lymphoma was previously regarded as SPTCL. The “SPTCL” subtype in this meta-analysis thus refers to alpha–beta SPTCL, and gamma delta T-cell lymphoma, until the publication by Willemze et al. [31] and the separation of these disease entities in the classification. However, these changes do only slightly affect the results of the meta-analysis. Additionally, the diagnostic strategies and the antibodies used for immunohistochemistry may differ between and even within countries.

Future studies on CTCL 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. An independent central review of the included cases could ensure the use of the same classification system and improve the precision of the diagnosis. All these suggestions are already being implemented in the Prospective International Cutaneous Lymphoma Prognostic Index (PROCLIPI) cohort study [39]. However, similar registries are also urgently needed on a national level and for lymphoma subtypes other than MF/SS.

4. Materials and Methods

A systematic review and meta-analysis was conducted based on a previously registered and published protocol [51] and according to the preferred reporting of items for systematic reviews and meta-analyses (PRISMA) [52].

4.1. Literature Search and Selection

A literature search was conducted based on a standardized strategy [51] in Medline via Pubmed and the Cochrane Library (Table S1). The identified records were screened by two independent reviewers (AM and GD) for eligibility. Reference lists of included studies were screened for additional records. Inclusion criteria were publication in a peer-reviewed journal (1) after 1999 (2) and reporting at least three subtypes (3) of primary cutaneous lymphomas (4) in at least 100 patients (5). Studies focusing on special populations (e.g., children or HIV-infected individuals) were excluded. Only English-, French-, German- or Spanish-language studies were included. The last date of the literature search was 29 July 2019.
4.2. Data Extraction and Quality Appraisal

The following information was extracted from the included studies by two independent reviewers: authors, year and title of publication, country and continent of the enrolled patients, time of enrolment, absolute and/or relative numbers of each primary cutaneous lymphoma subtype, staging, survival, used classification system (World Health Organization (WHO) [34], European Organization for Research and Treatment of Cancer (EORTC) [33] or WHO-EORTC [31]) and whether the data were considered representative by the authors. The reporting quality of included studies was rated by two independent reviewers (GD, AM) based on criteria derived from the IHE QA Checklist [53] and rated as present or absent. Items included the prospective/retrospective inclusion of patients, a single center/multicenter cohort and the consecutive inclusion of patients. A reporting bias was considered to be present if multiple CTCL subsets according to the classification were grouped together (e.g., no differentiation between mycosis fungoides (MF) and Sézary syndrome (SS)). Studies with an important number of unclassified cutaneous lymphomas or using various classification systems were considered as having a classification bias. We considered that reporting bias did not affect the cumulative evidence since we handled epidemiologic data of rare diseases.

4.3. Statistical Analysis

The absolute numbers of CTCL and CTCL subsets were extracted from the publications. Missing data were calculated within the same publication, if possible. We calculated the numbers in the following three subgroups: MF-SS (classical MF, MF variants and SS), CD30-positive lymphoproliferative disorders (LPD) (anaplastic large cell lymphoma (ALCL) and lymphomatoid papulosis (LyP)), adult T-cell lymphoma/leukemia (ATLL) and rare CTCL (as described by Willemze 2005 [31], including subcutaneous panniculitis-like T-cell lymphoma (SPTCL)). Due to the various numbers of included patients per study, the statistical analyses were performed on relative frequencies (proportions), e.g., cases of MF relative to the total number of CTCL. Proportions were checked for heterogeneity, and were combined using random-effects models to give estimates of the overall proportions. We also investigated whether proportions were consistent across geographic regions. For each region, subgroup proportions were computed. These were then combined across regions using a random effects meta-analysis. To normalize the distributions and to calculate the 95% confidence intervals, the Freeman–Tukey double arcsine transformation was used [54,55]. Statistical analysis was conducted using R Statistics [56] and the Metafor package [57].

5. Conclusions

In conclusion, our global meta-analysis of CTCL confirmed the predominance of CTCL among cutaneous lymphomas (83% on average) in the three analyzed continents, most of which were MF cases. It revealed the stability of SS and ALCL frequencies across continents, and the heterogeneity of MF, suggesting the possible role of environmental factors in the pathophysiology of the latter. International studies with a central clinico-histological review of cases, such as that initiated by the Cutaneous Lymphoma International Consortium (PROCLIP) [58], are extremely valuable in allowing a prospective analysis of CTCL frequencies, outcomes and prognostic factors worldwide. In addition to such international projects, prospective national registries are urgently needed.

Supplementary Materials: The following are available online at http://www.mdpi.com/2072-6694/12/10/2921/s1, Table S1: Search strategy, Table S2: Excluded studies with reasons for exclusion, Figure S1: Periods of subject enrolment and used classification systems, Figure S2: Meta-analysis of main CTCL groups compared to CTCL, Figure S3: Meta-analysis of the proportion of mycosis fungoides (MF) variants compared to CTCL, Figure S4: Meta-analysis of the proportion of CTCL, other than MF compared to CTCL.

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