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REVIEW ARTICLE

Updated review on prognostic factors in mycosis fungoides and new skin lymphoma trials

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Abstract

Background: Ten-year survival rates in mycosis fungoides (MF) broadly varies, however, there is no standardized prognostic index available. This is presumably due to low prevalence, heterogeneity, and diagnostic challenges in MF. Recent studies have focused on identifying objective prognostic indices by using different parameters for survival determinants. The Cutaneous Lymphoma International Prognostic Index (CLIPI) and the Prospective Cutaneous Lymphoma International Prognostic Index (PROCLIPI) represent prototypical studies that identify prognostic factors, seeking to improve management and outcomes in early-stage MF. Detecting these factors and stratifying MF patients according to their disease progression risk may help to manage these patients more efficiently.

Aims: Review the current literature to determine the risk factors determining prognosis in MF.

Methodology: A Comprehensive literature search was performed using electronic online databases "PubMed" and "Google Scholar" using key words 'prognostic factor', 'prognostic indicator', 'mycosis fungoides', 'Sezary syndrome', 'Skin Lymphoma', 'Cutaneous Lymphoma'. Articles published in English language were considered for the review.

Results: The strongest prognostic factor in MF patients is the stage of the disease. T stage and the presence of extracutaneous disease are the most important factors for survival. Other factors that are associated with worse prognosis are male gender, age >60, presence of plaques, folliculotropism, eosinophilia and lymph node stage above N1/Nx. Elevated LDH was associated with later tumor stages and large cell phenotype at diagnosis had a better prognosis. KIR3DL2 was associated with malignant transformation.

Conclusion: The PROCLIPI study has assessed risk factors collected in MF patients from different countries and across different ethnicities following a rigorous clinicopathologic process. The findings presented here illustrated that disease prognosis in

early stages depends on many contributing factors. Detection and stratification of such factors may allow a personalized approach to management of these patients.

KEYWORDS
cutaneous lymphoma international prognostic index, mycosis fungoides, prospective cutaneous lymphoma international prognostic index, skin lymphoma

1 | INTRODUCTION

Cutaneous T-cell lymphomas (CTCL) are a heterogeneous group of non-Hodgkin lymphomas characterized by skin-homing neoplastic T cells. Mycosis fungoides (MF) is the most common form of CTCL (54–72%). The overall annual age-adjusted incidence of CTCL is 6.4×10^{-6}. Incidence rate is higher among African Americans compared to Caucasians (9.0×10^{-6} vs 6.1×10^{-6}) and higher among males compared to females (8.7×10^{-6} vs 4.6×10^{-6}) (2). Median age at diagnosis is 55–60 years.[1]

Staging of MF is based on skin (T), lymph node (N), visceral (M), and blood (B) involvement (TNMB). Of these stages, T stage and the presence of extracutaneous disease are the most important factors for survival.[2] Early-stage disease (IA-IIA) portends a good prognosis compared to advanced stage disease (IIB-IVB). The predicted 10-year overall survival (OS) rates are 90.3% and 53.2% for early and advanced stage disease, respectively.[3] Early-stage disease (IA–IIA) presents with scaly patches alone (T1a/T2a) or patches and plaques (T1b/T2b) of different shapes and sizes, mostly located on the sun-protected areas of the body. Early-stage disease mimics a variety of skin conditions, with mean delay of 36 months from the time of onset to the final diagnosis.[4] Up to one third of patients with early-stage disease may progress to advanced disease.[5] Advanced stage disease presents with widespread patches or plaques with internal organ and/or blood involvement. Three percent of patients with MF progress to Sezary syndrome (SS). SS is a leukemic form of CTCL, which presents with erythroderma, generalized adenopathy, and peripheral blood involvement.[6]

Prognostic factors in MF are less well-defined compared to other lymphomas due to lack of large cohorts, disease rarity, and diagnostic challenges.

Recently, the cutaneous lymphoma international prognostic index (CLIPI) has been developed to predict prognosis in early and advanced stages, based on data collected from a cohort of 1502 patients from United Kingdom.[7] These data showed male gender, folliculotropism, advanced age (>60), and nodal involvement N1/Nx for poor prognostic factors in early-stage MF. Likewise, advanced age, B1/B2 blood involvement, N2/N3 nodal involvement, and visceral involvement contribute to poor prognosis in advanced stage MF. The Cutaneous Lymphoma International Consortium presented the findings of their newly established Prospective Cutaneous Lymphoma International Prognostic Index (PROCLIPI) international registry for early-stage MF.[4] In this study, researchers used approximately 1000 patients' data from 29 countries worldwide, to investigate clinical, hematological, radiological immunohistochemical, genotypical data as well as health-related quality of life scores. Herein, we aimed to review the recent literature to determine the prognostic factors for early and advanced stage disease.

2 | PROGNOSTIC INDICES IN MYCOSIS FUNGOIDES

The strongest prognostic factor in MF patients is the stage of the disease. T stage and the presence of extracutaneous disease are the most important factors for survival.[2,8] Other factors that are associated with worse prognosis are male gender, age >60, presence of plaques, folliculotropism, and lymph node stage above N1/Nx. Using these variables, Cutaneous Lymphoma International Consortium has developed prognostic indices as described in the CLIPI study. MF patients are classified into three groups according to patients' risk for disease progression defined as low, intermediate, and high. Ten-year OS rates were 90.3%, 76.2%, 48.9% for low, intermediate, and high-risk patients in early-stage disease.[3]

3 | SKIN INVOLVEMENT AND PROGNOSIS

In the PROCLIPI and CLIPI studies, contributors used the modified severity weighted assessment tool (mSWAT), which is a method for measuring skin tumor burden and may be used to monitor disease progression in patients under treatment. In this method, the extension of lesion (patches, plaques, tumors) is measured according to the body surface area (BSA) involved. BSA is calculated using the palm and fingers of the patient method, where each hand represents 1% of the total BSA of the patient. A subsequent multiplication factor of x1 for patch, x2 for plaque, and x4 for tumors and the sum of all lesions are calculated. mSWAT score ranges from zero to 400, and median scores increase as the stage progresses.[8]

Plaque lesions were determined to be an independent risk factor for poor survival in early-stage disease in CLIPI study which included 1057 patients[3] whereas patch lesions are associated with better survival compared to plaque lesions.[9] Agar et al.[10] found that stage IB/IIA patients (patches/plaques over 10% of BSA without extracutaneous involvement) had a median survival of 11 years. Approximately 25% of them progressed to more advanced stages, and 20% of them died of causes related to MF.

In the PROCLIPI study, 348 patients were diagnosed with early-stage MF (IA-IIA). Forty-six percent of the patients had only patches,

whereas 39.1% of the patients had coexistent patches and plaques and were more frequently seen with extensive skin involvement: 46.5% in IA compared to 57.7% in IB. The frequency of poikiloderma and hypopigmentation was found to be similar in all stages.[2] It remains to be determined whether the extent of disease, type of primary lesion, and presence of poikiloderma and hypopigmentation affect disease outcomes.

4 | AGE AND PROGNOSIS

MF commonly presents in older individuals with a peak incidence between the 6th–7th decades of life but can begin as early as 1st decade. In the PROCLIPI study, the median age of diagnosis was 57 years in early-stage MF without any difference between the groups. Age at diagnosis in early-stage MF was significantly lower than age at diagnosis in advanced stage disease.[4] Prognosis of the disease strongly depends on the age at diagnosis. Older age is associated with poorer prognosis.[11] Crowley et al. compared patients diagnosed with MF before 35 years of age with classical MF patients. Patients who had been diagnosed before 35 years of age had limited patch/plaque lesions (T1), less erythroderma (T4), and had a better prognosis compared to older individuals.[12] When controlled for T stage, however, age did not predict survival.[12] In another study, patients diagnosed with MF under the age of 30 had favorable prognosis compared to older individuals, but there was an increased risk of secondary malignancies, especially melanoma and lymphoma.[13]

5 | SEX AND PROGNOSIS

MF incidence and disease course differs based on sex. Males have a higher incidence, 5.6/1 000 000 compared to 3.6/1 000 000 in females. Males generally are diagnosed at higher T stages compared to females.[14] The CLIPI study supported this observation and found that males have worse prognosis that females regardless of disease stage.[7] Data from the PROCLIPI study results were consistent with these findings, showing a male-to-female incidence ratio of 1.7/1. Males in the PROCLIPI study also showed higher tumor stages.[4]

6 | NODAL INVOLVEMENT IN EARLY-STAGE DISEASE AND PROGNOSIS

Clinically abnormal lymph nodes are defined as more than 15 mm in diameter or firm, irregular, clustered or fixed, regardless of the size. In early-stage MF patients, lymph node status is denoted by N0 through N3. N0 represents no abnormality, N1 represents dematopathic lymph nodes, and N2 represents early nodal involvement with aggregated atypical T cells and preserved nodal architecture. N3 represents the loss of lymph node architecture and is considered advanced stage disease (IVA2- IVB). Clinically abnormal lymph nodes without biopsy are considered to be Nx.[8] N1 involvement had significantly lower overall survival (relative risk of 2.8) compared to N0.[15] N2 involvement has worse prognosis compared to N0/N1, with survival rates similar to those patients with N3 nodal involvement (stage IVA2).[10] Assessment of T-cell receptor clonality in excised lymph nodes is highly recommended in MF patients. Nodal involvement can be subcategorized into negative or positive clonality categories. Positive clonality is associated with worse prognosis but does not affect disease staging.[16,17]

Twenty-three early-stage MF patients enrolled in PROCLIPI had enlarged lymph nodes on imaging. Lymph nodes were mostly present at peripheral sites, including inguinofemoral (69.5%), axillary (56.6%), and cervical (21.7%). The study recorded the number of nodal sites with enlarged LNs and proposed a scoring system with values ranging from 0 to 8. The total nodal score is correlated with survival and could be related to prognosis.[2]

7 | LACTATE DEHYDROGENASE LEVELS AND PROGNOSIS

Lactate dehydrogenase (LDH) is a cytoplasmic enzyme that catalyzes the conversion of lactate to pyruvate in the last step of glycolysis. Lactate levels are increased in many tumors, leading to tumor microenvironment acidification, angiogenesis, tumor progression, and metastasis.[18] High LDH levels are a poor prognostic factor in non-Hodgkin lymphoma (NHL), and survival rate is negatively correlated with serum LDH levels regardless of other clinical parameters.[19] In MF, LDH is a non-specific marker of tumor burden and has been associated with poor prognosis in advanced stage[20]; however, the predictive value of LDH levels in early-stage patients is not clear.[21]

Al Saif et al. conducted a study to investigate LDH levels in MF patients. Stage IB, IIA, and advanced stage patients showed elevated LDH levels (20%, 50%, and 100%, respectively), whereas stage IA patients had normal levels of LDH.[22] Diamandidou et al.[23] concluded raised serum Beta-2 microglobulin and LDH levels were predictive of LCT in early-stage MF patients. In another study including 161 patients, no significant differences in LDH levels were observed between stage IA and other stages.[24] In PROCLIPI study, LDH levels were elevated in 27 of the patients with early-stage disease. Stage IIA showed higher LDH levels (43.5%) compared to stage IA and IB (6.7% and 8.9%, respectively).[4] In folliculotropic MF patients, elevated LDH levels were associated with 5.53 times increased mortality compared to FMF patients with normal LDH levels.[25]

8 | LARGE CELL TRANSFORMATION AND PROGNOSIS

Large cell transformation (LCT) is defined by the presence of CD30− or CD30+ large cells (at least 4 times larger than a small lymphocyte) exceeding 25% of the infiltrate or forming microscopic nodules. Large cell transformation is seen in 20–50% of advanced MF patients.[26–28] In patients with LCT, mean 5-year survival is less than 20%.[27] Early

LCT occurring <2 years from diagnosis as well as LCT occurring at advanced stage disease is associated with poor prognosis.[23] Pulitzer et al.[29] reviewed histology slides to identify prognostic factors in 51 MF patients with LCT. Interestingly, this study showed that patients with LCT at the time of diagnosis had a better survival compared to those who had a small cell phenotype. They also found that the presence of fibrosis at LCT was associated with increased survival.

9 | EOSINOPHILIA AND PROGNOSIS

Mycosis fungoides is frequently associated with eosinophilia. Eosinophilia has been attributed to Th2 predominance leading to interleukin-5 (an eosinophilotactic cytokine) expression by neoplastic T cells.[30,31] In MF, Th1 cells play a key role for initiation and maintenance of anti-tumor response against neoplastic T cells. Th2 predominance is associated with reduced antitumoral response in MF lesions.[32] According to these findings, eosinophilia has been investigated as a prognostic factor in MF patients. A few studies showed a decreased survival and increased disease progression rate in cases of MF with eosinophilia.[31,32]

10 | FLOW CYTOMETRY AND PROGNOSIS

Detecting blood involvement is important as the MF stage progresses to extensive T2 stage. The presence in blood of T-cell clones identical to skin clones is a qualitative diagnostic criterion for MF. Search for circulating Sezary cells is essential to determine the stage and the prognosis. Flow cytometry (FC) has largely supplanted the microscopic Sezary cell count of the peripheral blood, enabling a more accurate analysis. FC is an objective and standardized method to quantify Sezary cells in the peripheral blood for staging MF patients. Sezary cells phenotypically identified as CD4+, CD7− or CD4+, CD26− in the peripheral blood in FC analysis. Assessment of blood involvement is categorized as B0 when Sezary cell count is <250/mm^3 and B1 if Sezary cell count is 250/mm^3–1000/mm^3. To diagnose B2 stage, T-cell receptor clonal rearrangement in blood as well as one of the following criteria is required: Sezary cell count >1000/mm^3, CD4/CD8 > 10, loss of CD7 expression >40% or CD 26 expression >30%.[33]

Another emerging peripheral blood marker for prognosis is KIR3DL2.[34] KIR3DL2 is a recently discovered marker for malignant clonal cell population in patients with SS, which is an independent poor prognostic factor in MF patients. Clinical studies have found this molecule as a useful tool for diagnosis, prognosis, and guiding patient follow-up.[35]

11 | T-CELL RECEPTOR CLONALITY AND PROGNOSIS

Some studies have shown that clonality in T-cell receptor gene rearrangement may be factor predicting poor prognosis. Patients who presented with clonal TCR gene rearrangement in skin and peripheral blood had a worse prognosis than patients with non-matching clones.[10] Furthermore, a cell clone frequency of more than 25% was an independent negative prognostic factor for early-stage MF.[36]

In PROCLIPI study, T-cell receptor gene analysis was performed in 205 patients. 64.4% showed clonality, with a similar percentage in early-stage patients. Contributors concluded that clonality is not a reliable sensitive diagnostic test considering the heterogeneity of the methods that have been used to detect T-cell clones. However, clonality data will continue to be collected for further analysis.[2]

12 | QUALITY OF LIFE AND PROGNOSIS

There is an effort to develop health-related quality of life measurement instruments in MF patients. Pruritus, which occurs in approximately 50% of MF patients, commonly causes distress and is prevalent even in early disease stages. To assess the impact on quality of line, assessment tools such as Skindex-29, ItchyQol (Itch related Quality of Life Index) and Fact-G scores have been developed. There is a significant overlap between Skindex-29 scores and pruritus scores. Similarly, disease stage is positively correlated with itch intensity and itch-related quality of life impairment.[37]

PROCLIPI also assessed the quality of life of MF patients and health-related quality of life (HRQol) using the Skindex-29 score. Median HRQoL scores lie in the severe range for MF/SS patients compared to benign dermatosis and non-melanoma skin cancer.[38] Patients with advanced stage disease have overall worse HRQoL compared to early-stage patients. HRQoL as measured using Skindex-29 correlated with extent of skin disease as measured by mSWAT score.

When analyzed by subgroup, the HRQoL was worse in female patients with SS, in advanced stage disease, in patients with elevated LDH levels, and in those with alopecia. Compared to male patients, female patients were more likely to report severe impairment with symptoms like burning, stinging, pruritus, and irritation and suffered from depression, shame, embarrassment, and annoyance with their MF/SS diagnosis.[39] Alopecia and confluent erythema are visual clinical features that may affect a patient's self-confidence and body image and may lead to social isolation and depression.

Illness perception, which is a concept that represents an individual's understanding and interpretation of disease, has been investigated as a parameter that could influence behavior and health-related quality of life in MF patients. Recognition of illness perception and subsequent effects on quality of life in MF patients might lead to improved adherence to treatment by increasing support for patients according to their needs.[40] In addition, researchers report that as illness perceptions change rapidly with diagnostic results, indicating that illness perception may be used as a marker of therapeutic success. Studies have not found any difference in illness

perception between males and females in MF patients. This could be attributed to male predominance in this study. Females tend to perceive their disease as more chronic and report that they are more affected emotionally than males.[41] The PROCLIPI study demonstrated that females reported more severe symptoms and suffered from a higher emotional burden, though male gender was associated with poorer prognosis.[11]

13 | FOLLICULOTROPIC MYCOSIS FUNGOIDES AND PROGNOSIS

Folliculotropic MF (FMF) is a distinct and less common variant of MF, histologically characterized by infiltration of atypical T lymphocytes of the hair follicles. FMF may differ from classic MF prognostically. Thus, our approach with patients with FMF perhaps should be different from classic MF.[42]

Patients with conventional MF usually present with patch or plaque-type lesions on sun-protected areas of the skin. FMF can present like classic MF with patches, plaques, tumors, and erythroderma. However, FMF can also manifest with acneiform lesions, grouped follicular lesions, and plaque lesions involving the head and neck and extremities.[25,43] In one study, head and neck involvement was observed in 75% of FMF patients with advanced stage and was associated with poor prognosis.[25] In FMF lesions located on the head and neck, pronounced plaques may develop into tumors and cause alopecia.[44] Previous studies have reported an alopecia rate between 21–81% among FMF patients and head and neck involvement was related to tumoral lesions.[45] Thus, presence of alopecia is considered a poor prognostic factor in patients with folliculotropic MF. Previously, FMF was considered to have a worse prognosis than conventional MF.[46] Subsets of FMF may have clinically indolent or aggressive behavior.[47]

In FMF, folliculotropism is commonly seen, with atypical neoplastic infiltrate around hair follicles. In contrast to conventional MF, epidermis is normal and no epidermotropism is observed. Another feature that may be seen in the histopathology of FMF is mucinous degeneration.[44] However, follicular mucinosis is not associated with survival or disease progression in FMF cases.[47]

Folliculotropic MF was previously thought to have worse prognosis to be worse than classic MF, with FMF patients being more refractory to treatment and more likely to progress to advanced stages. Van Santen et al. conducted a prospective cohort trial comparing FMF cases to conventional MF cases. In general, patients with FMF were found to be more likely to be refractory to treatment with cutaneous directed therapies. The survival in FMF patients was significantly worse than plaque-stage MF patients.[48] However, when comparing FMF and tumor stage MF, survival was not significantly different. This suggests that FMF patients should be managed as tumor stage MF patients.[42] There were other large retrospective studies including over 1500 patients, and these studies showed that FMF was associated with increased risk of disease progression.[10] Conversely, smaller case series suggested that a subset of FMF might be associated with good prognosis, but they lacked definite criteria which could define the subset.[43,49] To answer this question, the Dutch Cutaneous Lymphoma Group conducted a prospective cohort study with 203 MF patients. The folliculotropic lesions presenting as patches and grouped follicular papules, behaved like early-stage MF. In contrast, tumor lesions behaved rather like advanced stage classic MF.[30] Although FMF lesions may clinically look similar, there are histological differences. Some plaque lesions had sparse infiltrate with small neoplastic T cells and were defined as early plaque-stage FMF. In comparison, lesions with denser infiltrate with medium/large neoplastic T cells were designated advanced plaque-stage FMF.[50] Advanced age at the time of diagnosis and LCT are associated with higher risk of disease progression and poor survival.[30] Another single-center study showed that FMF is rapidly progressive compared to classical MF, with OS rates of 68% and 28% for these cases, respectively. FMF was seen more commonly in males with high pruritus scores and with extracutaneous disease.[51] Most FMF cases (69%) showed follicular mucinosis on histology and this might have contributed to worse prognosis.[42]

The CLIPI study included 189 patients with FMF. These patients demonstrated significantly higher risk of disease progression; however, OS and disease-specific survival (DSS) rates were similar to the MF group.[10] Talpur et al.[52] conducted a study including 44 patients with FMF, and the folliculotropic variant was not an independent determinant for progression-free survival (PFS), disease-specific survival (DSS), or OS. Giberson et al.[53] reported that there is no difference in OS between FMF and MF. In this study, negative predictors of OS were age, male gender, advanced stage, and lack of initial response to PUVA treatment. In PROCLIPI study, 17.8% of the patients were diagnosed with FMF and these patients were more likely to be stage IB/IIA than IA.[4] A recently published study from the United States found that the cutaneous stage was only the significant parameter for predicting DSS. This study also confirmed that FMF is a heterogenous disease divided into early and advanced stages, and poorer prognosis is associated with advanced cutaneous stage.[54]

14 | CONCLUSION

Mycosis fungoides is a rare disease with poorly understood biology and a broad range of clinical presentation and outcomes. Because longitudinal data are scarce, prognostic indicators are ill-defined. Thus, there is a need for validated prognostic tools to assess disease progression risk among heterogeneous groups of MF patients. The PROCLIPI study has assessed such risk factors collected in MF patients from different countries and across different ethnicities following a rigorous clinicopathologic process. The findings presented here illustrated that disease prognosis in early stages depends on many contributing factors. Detection and stratification of these factors may allow a personalized approach to management of these patients. There is a tremendous effort underway to validate these and other

factors to stratify patients into risk groups in the near future. The PROCLIPI study is a prototypical study that is essential in contributing to this goal.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Banu Farabi: Writing and revising the manuscript. Lucia Seminario-Vidal, Marielle Jamgochian, Bengu Nisa Akay, Mehmet Fatih Atak, Babar K. Rao, Priyanka Karagaiah, and Stephan Grabbe: Review and revising the manuscript. Mohamad Goldust: Conception, writing, review, and revising the manuscript.

DISCLAIMER

We confirm that the manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work.

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ETHICAL APPROVAL

No ethical approval was needed in this review work.

DATA AVAILABILITY STATEMENT

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

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