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ORIGINAL REPORT

Cutaneous Lymphoma International Consortium Study of Outcome in Advanced Stages of Mycosis Fungoides and Sézary Syndrome: Effect of Specific Prognostic Markers on Survival and Development of a Prognostic Model

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ABSTRACT

Purpose
Advanced-stage mycosis fungoides (MF; stage IIB to IV) and Sézary syndrome (SS) are aggressive lymphomas with a median survival of 1 to 5 years. Clinical management is stage based; however, there is wide range of outcome within stages. Published prognostic studies in MF/SS have been single-center trials. Because of the rarity of MF/SS, only a large collaboration would power a study to identify independent prognostic markers.

Patients and Methods
Literature review identified the following 10 candidate markers: stage, age, sex, cutaneous histologic features of folliculotropism, CD30 positivity, proliferation index, large-cell transformation, WBC/lymphocyte count, serum lactate dehydrogenase, and identical T-cell clone in blood and skin. Data were collected at specialist centers on patients diagnosed with advanced-stage MF/SS from 2007. Each parameter recorded at diagnosis was tested against overall survival (OS).

Results
Staging data on 1,275 patients with advanced MF/SS from 29 international sites were included for survival analysis. The median OS was 63 months, with 2- and 5-year survival rates of 77% and 52%, respectively. The median OS for patients with stage IIB disease was 68 months, but patients diagnosed with stage III disease had slightly improved survival compared with patients with stage IIB, although patients diagnosed with stage IV disease had significantly worse survival (48 months for stage IVA and 33 months for stage IVB). Of the 10 variables tested, four (stage IV, age $>$ 60 years, large-cell transformation, and increased lactate dehydrogenase) were independent prognostic markers for a worse survival. Combining these four factors in a prognostic index model identified the following three risk groups across stages with significantly different 5-year survival rates: low risk (68%), intermediate risk (44%), and high risk (28%).

Conclusion
To our knowledge, this study includes the largest cohort of patients with advanced-stage MF/SS and identifies markers with independent prognostic value, which, used together in a prognostic index, may be useful to stratify advanced-stage patients.

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INTRODUCTION

Cutaneous T-cell lymphomas are a family of extranodal lymphomas of mature T cells presenting in the skin. Mycosis fungoides (MF) is the most common form, and Sézary syndrome (SS) is a less frequent erythrodermic variant with leukemic involvement. The revised staging system from 2007[1] classifies disease presentation in skin (T), lymph nodes (N), viscera (M), and blood (B). This TNMB classification stratifies patients into those with early-stage (stage IA to IIA) or advanced stage (stage IIB to IVB) disease (Appendix Table A1, online only). Early stage carries a good prognosis, with survival often exceeding 10 years.[1-3] A third of patients present with advanced skin disease (T3-4), with median survival times of 35 to 56 months, or nodal disease (median survival, 13 to 25 months). Involvement of viscera is rare. Survival according to stage has been reported from centers, with 5-year overall survival (OS) rates of 40% to 65% for stage IIB, 40% to 57% for stage III, 15% to 40% for stage IVA, and 0% to 15% for stage IVB, whereas at 10 years, up to 40% of stage IIB and III patients were alive.[4] In addition to stage, other potential prognostic markers have been identified in MF/SS. These include clinical features such as male sex and older age, elevated lactate dehydrogenase (LDH), and histologic features of folliculotropism (FT) and large-cell transformation (LCT).[5-11] Previous studies of prognostic factors have been mainly single-center studies, and only a large-scale international collaboration will allow the true impact of these factors to be defined.

A recent study that proposed a prognostic model of MF/SS based on a large data set (N = 1,502) from a single center in the United Kingdom with a validation set from a single center from the United States[12] prompted the establishment of the Cutaneous Lymphoma International Consortium (CLIC) consortium. CLIC includes board members from established cutaneous lymphoma groups, such as the European Organisation for Research and Treatment of Cancer Cutaneous Lymphoma Taskforce, International Society for Cutaneous Lymphomas, US Cutaneous Lymphoma Consortium, and United Kingdom Cutaneous Lymphoma Group, and aims to improve understanding of the clinical and translational aspects of these rare lymphomas through collaborative research, using uniform terminology and well-defined end points. We report the results of the initial CLIC[1] retrospective study designed to test the relevance of candidate prognostic markers on OS in advanced-stage MF/SS. The aim was to accurately identify patients with a worse outcome who may not be recognized in the current staging system with the intention of developing a prognostic index.

PATIENTS AND METHODS

Patient Selection and Staging

Specialist cutaneous T-cell lymphoma centers were contacted through membership of the major cutaneous lymphoma organizations (European Organisation for Research and Treatment of Cancer, International Society for Cutaneous Lymphomas, US Cutaneous Lymphoma Consortium, United Kingdom Cutaneous Lymphoma Group). This study was approved by a "mother center" institutional review board at Stanford University and also received local approval. Data were collected retrospectively on consecutive patients from patient records and existing databases. Eligible patients were those diagnosed with clinical stage IIB or higher disease from 2007.[1] Data were collated from centers and reviewed independently for data accuracy and completeness at University Hospital Birmingham and Stanford University. Missing or questionable data were assessed manually, and queries were resolved with centers.

Prognostic Parameters

After a series of CLIC teleconferences from 2012 to 2013 and literature review of prognostic markers in MF/SS,[4] the following 10 clinical, pathologic, and laboratory parameters were selected to study: stage, age, sex, histologic features (obtained from local reports) of FT,[2] LCT,[13] percentage of $CD30^+$ cells within the tumoral component, proliferation index measured by percentage of tumoral cells staining positive for Ki-67, WBC/absolute lymphocyte count (ALC), presence of an identical T-cell receptor clone in blood and skin, and serum LDH.[1] Each parameter was taken from time of initial diagnosis, and missing data were recorded as not done or not recorded.

Statistical Analysis

Percentage of data fields successfully captured at each site and pooled collated data were summarized. Actuarial OS and disease-specific survival for each stage and each prognostic parameter were calculated using the Kaplan-Meier method. Univariable associations were tested using log-rank tests. Multivariable analyses were performed using the Cox proportional hazards regression model. For multivariable analysis, all variables were included in the model selection process. A backward stepwise approach was taken to select variables with the most predictive power ($P < .10$). The proportionality assumption of the final model was tested using Schoenfeld residuals. Missing values were included in the model as an additional category because these may reflect the clinical decision not to perform certain tests. To capture some of the expected variation between centers, a dummy variable for each was included in the model but not reported on in this article. Prognostic markers identified were used in a prognostic model to identify risk groups for advanced MF/SS.

RESULTS

Cohort Characteristics

This study included 1,394 patients from 29 specialist centers (Europe, n = 19; North America, n = 7; Oceania, n = 1; South America, n = 1; Asia, n = 1; Table 1). One thousand two hundred seventy-five patients (91%) met the eligibility criteria for this study (stage IIB to IV disease diagnosed from 2007), and these patients were included in the survival analysis. Data completeness for the other 10 prognostic variables ranged from 36.9% to 99.2% (Table 2). Age and sex were recorded in 99.2% of patients. The median age of the group was 63 years (range, 8 to 98 years) with 789 males and 473 females.

Clinical Stage

Stage at diagnosis was IIB in 457, III in 320, IVA in 463, and IVB in 35 patients. The median OS time of the entire group was 63 months with 1-, 2-, and 5-year survival rates of 88%, 77%, and 52% (Table 3). The median OS times were 68 months in stage IIB, not reached in stage III, 47.5 months in stage IVA, and 33 months in stage IVB. Predicted 5-year OS rates are 57.4% for stage IIB, 58.2% for stage III, 42.9% for stage IVA, and 39% for stage IVB. Using stage IIB as a comparator, there was no significant difference in survival between stage IIB and stage III, and median OS was slightly improved in stage III patients (Fig 1). Survival for patients with stage IVA and IVB disease was significantly worse than that for patients with stage IIB disease ($P = .003$ and $P = .008$, respectively). OS and disease-specific survival rates, including 1-, 2-, and 5-year predicted survival according to stage, are listed in Table 3.

Appendix Figure A1 (online only) shows survival according to blood classification, which was available in 1,215 patients. The revised staging system for MF/SS (Appendix Table A1) segregates patients into stages IIIA, IIIB, and IVA1 according to extent of blood involvement (B0, B1, or B2), but compared with stage IIIA, survival differences for stage IIIB or IVA1 did not reach statistical significance

Table 1. Participating International Centers

Center No.	Principal Investigator	Address	No. of Patients
E 001	Julia Scarisbrick	University Hospital Birmingham, Birmingham, United Kingdom	35
E 002	Pietro Quaglino	University of Turin, Turin, Italy	50
E 004	Sean Whittaker	St Thomas' Hospital, London, United Kingdom	215
E 005	Maarten Vermeer	Leiden University Medical Centre, Leiden, the Netherlands	55
E 006	Richard Cowan	Christie Hospital, Manchester, United Kingdom	11
E 007	Evangelina Papadavid	Athens University Medical School, Athens, Greece	40
E 008	Pablo Oritz-Romero	Hospital 12 de Octubre, Madrid, Spain	23
E 009	Martine Bagot	Hospital St Louis, Paris, France	50
E 010	Rudolf Stadler	Johannes Wesling Medical Centre, Minden, Germany	10
E 011	Robert Gniadecki	Bispebjerg Hospital, Copenhagen University, Copenhagen, Denmark	33
E 012	Robert Knobler, Stefanie Pokert	University of Vienna Medical School, Vienna, Austria	7
E 018	Nicola Pimpinelli	University of Florence, Florence, Italy	22
E 019	Octavio Servietje	Hospital Universitari de Bellvitge, Barcelona, Spain	14
E 020	Emilia Hodak	Rabin Medical, Tel Aviv, Israel	30
E 021	Alessandro Pileri	University of Bologna, Bologna, Italy	14
E 022	Marie Beylot-Barry	Centre Hospitalier Universitaire Hospital de Bordeaux, Bordeaux, France	50
E 023	Teresa Estrach	Hospital Clinico, University of Barcelona, Barcelona, Spain	13
E 024	Emilio Berti	University of Milano, Milano, Italy	29
E 025	Ramon Pujol	Hospital del Mar Barcelona, Barcelona, Spain	12
NA 001	Youn Kim	Stanford University, Stanford, CA	121
NA 003	Steven Horwitz	Memorial Sloan-Kettering Cancer Center, New York, NY	46
NA 004	Joan Guitart	Northwestern University, Chicago, IL	46
NA 005	Madeleine Duvic	The University of Texas MD Anderson Cancer Center, Houston, TX	164
NA 006	Pierluigi Porcu	Ohio State University, Columbus, OH	11
NA 010	Francine Foss	Yale University, New Haven, CT	40
NA 011	Alain Rook	University of Pennsylvania, Philadelphia, PA	16
OC 001	Miles Prince	Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia	56
AS 001	Makoto Sugaya	Faculty of Medicine, University of Tokyo, Tokyo, Japan	29
SA 001	José Antonio Sanches	University of Sao Paulo Medical School, Sao Paulo, Brazil	33

Abbreviations: AS, Asia; E, Europe; NA, North America; OC, Oceania; SA, South America.

(Appendix Fig A2, online only). Stage IVA2 includes patients with partial or complete effacement of nodal architecture with atypical lymphocytes (N3). Median survival was 29 months in stage IVA2, with a 5-year survival rate of 32.9%. In comparison, stage IVA1 had a median survival time of 53 months and a 5-year predicted survival rate of 48.3% ($P < .001$; Table 3). Comparing OS across continents and in patients from the United States versus outside of the United States, there were no significant differences in survival according to stage.

Prognostic Markers

In univariable analyses, stage IV, age greater than 60 years, absent FT, LCT in skin, elevated WBC, and elevated LDH were identified as adverse prognostic factors. Table 2 lists the number of patients, survival ranges, and probability of survival at 1, 2, and 5 years for each parameter.

Age greater than 60 years (n = 813) was associated with a significantly worse OS ($P < .001$) and a median survival time of 52 months. Using age $\leq$ 60 years as the reference category, the hazard ratio for survival was 1.35 (95% CI, 1.04 to 1.75) in patients age 60 to 70 years and 1.91 (95% CI, 1.48 to 2.45) in patients age $\geq$ 70 years. Age was also significant as a continuous variable (hazard ratio, 1.03; 95% CI, 1.02 to 1.04; $P < .001$), so for every year increase in age, the hazard increased by 3%. The male-to-female ratio was 1.7:1, with no difference in survival according to sex.

FT was present in 17.2% of 1,062 FT-evaluable patients. In univariable analysis, those with absent FT in skin had a significantly worse prognosis than those with FT ($P < .001$). LCT in skin was present in 19.6% of 1,098 LCT-evaluable patients at diagnosis (including > 50% with stage IIB disease). LCT in skin was independently associated with a worse prognosis ($P = .003$), with an OS of 49.8 months and 5-year survival of 39%. There was no association between LCT and FT. $CD30^+$ and Ki-67 positivity were intended to be recorded as absolute percentages, but a number of centers only recorded a range. Percentages of $CD30^+$ and Ki-67 positivity of more than 10% and more than 20%, respectively, were considered positive, which allowed most data to be included. The cutoff is arbitrary because no percentage number has been agreed upon in MF/SS and varying percentages of positivity are reported.[14] $CD30^+$ was present in 149 patients (23.3%), and Ki-67 positivity was present in 182 patients (38.6%). No difference in survival between patients positive or negative for CD30 or Ki-67 was shown for the cohort, but in T3 disease, both $CD30^+$ and Ki-67 positivity were significantly associated with a worse survival ($P < .001$ and $P = .04$, respectively).

Elevated WBC count was associated with a worse prognosis, with a median survival time of 38 months versus 54 months in patients without an elevated WBC count ($P = .006$). Elevated ALC did not carry a significantly worse prognosis for the whole cohort or those with T4 disease ($P = .358$ and $P = .4$, respectively). Four hundred fifty-seven patients (62%) had a documented blood clone, and this was identical to the skin clone in 357 patients (49%). Patients with an identical blood clone had a worse prognosis, with a median survival of 49.8 months compared with 73.4 months in patients without an

Table 2. Number of Patients, Survival Ranges, and Probability of Survival With Univariable Analysis for the 10 Parameters Tested

Variable	No. of Patients With Complete Data (%)	No. of Patients	OS (months)			RM Survival (months)	Probability of Survival (%)			*P*
			Median	95% CI	IQR		1 Year	2 Years	5 Years	
Sex	1,262 (99.0)									.937
Male		789	63.0	52.7 to 73.7	25.0-NR	56.2	87.3	76.0	52.1	
Female		473	60.3	49.8 to 70.5	26.1-NR	55.8	89.3	77.3	50.4	
Age, years	1,265 (99.2)									< .001
≤ 60		452	NR	NA	34.2-NR	63.6	92.8	84.7	62.5	
> 60		813	51.0	45.2 to 61.0	21.7-NR	51.7	85.4	71.9	45.6	
FT	1,062 (83.3)									< .001
Absent		879	57.5	47.7 to 65.4	24.4-NR	54.6	87.9	75.2	49.3	
Present		183	NR	NA	44.8-NR	65.9	91.4	86.6	66.5	
WBC count	716 (56.2)									.006
Elevated		252	37.7	30.2 to 50.0	17.8-78.8	44.3	85.8	67.5	35.3	
Not elevated		436	54.4	44.4 to 65.4	24.8-NR	53.8	87.9	75.8	46.1	
Low		28	57.5	34.4 to NR	34.4-NR	60.0	95.5	84.9	48.8	
Absolute lymphocyte count	847 (66.4)									.358
Elevated		248	52.7	42.7 to 78.8	24.5-NR	53.5	88.8	76.8	49.5	
Not elevated		485	57.3	46.4 to 67.9	23.4-NR	54.7	87.8	74.1	48.4	
Low		114	42.2	34.4 to 65.4	18.6-NR	47.4	82.0	72.0	37.8	
LDH	894 (70.1)									< .001
Elevated		457	44.7	37.5 to 50.5	19.2-NR	48.6	84.6	68.6	39.0	
Not elevated		437	78.8	61.2 to NR	33.2-NR	60.5	90.9	81.9	58.4	
TCR clone	727 (57.0)									.086
Identical clone in blood and skin		357	49.8	44.7 to 69	24.4-NR	53.8	88.4	76.2	45.6	
No identical clone in blood and skin		370	73.4	61.0 to NR	30.2-NR	59.3	87.1	78.5	58.7	
LCT	1,098 (86.1)									.003
Yes		215	49.8	40.3 to 57.3	20.1-NR	48.9	84.8	68.6	38.5	
No		883	66.2	61.0 to NR	27.7-NR	57.8	89.3	78.4	54.9	
CD30	639 (50.1)									.331
Positive > 10%		149	55.7	45.4 to NR	22.3-NR	54.9	88.6	74.6	44.9	
Positive ≤ 10%		490	68.7	60.3 to NR	28.0-NR	58.7	87.8	78.2	56.7	
Ki-67	471 (36.9)									.552
Positive > 20%		182	50.1	44.8 to NR	25.2-NR	55.9	89.3	76.9	46.8	
Positive ≤ 20%		289	NR	47.2 to NR	30.8-NR	58.7	86.7	78.6	55.6	

Abbreviations: FT, folliculotropism; IQR, interquartile range; LCT, large-cell transformation; LDH, lactate dehydrogenase; NR, not reached; OS, overall survival; RM, restricted mean; TCR, T-cell receptor.

identical blood clone ($P = .086$). Serum LDH was elevated in 457 patients (51.1%). An elevated LDH was an adverse risk factor, with a median survival time of 44.7months compared with 78.8 months in patients with a normal LDH ($P < .001$).

Prognostic Index Model

In multivariable analysis, stage IV disease ($P = .009$), age greater than 60 years ($P < .001$), LCT in the skin ($P < .001$), and elevated serum LDH ($P < .001$) were all independent prognostic variables for worse survival. Using these four variables, we built a prognostic index model in the subset of patients with a complete data set (N = 857; IIB, n = 277; III, n = 220; IV, n = 360), where zero or one variable equals low risk, two variables equal intermediate risk, and three to four variables equal high risk. This model distinguishes risk groups across stage, with 5-year predicted OS rates of 67.8% (low risk), 43.5% (intermediate risk), and 27.6% (high risk; $P < .001$, Table 4, and Fig 2).

DISCUSSION

To our knowledge, this study represents the largest reported cohort of patients with advanced-stage MF/SS (n = 1,275). It involves an unprecedented scale of international collaboration including patients from 29 centers spanning five continents. The results confirm poor survival in patients with advanced MF/SS, with a median OS of 63 months, 2-year survival of 77%, and 5-year survival of 52%. Using stage IIB as the comparator (median OS, 68 months), we were unable to fully validate the revised staging; survival in stage IIIA was in fact slightly improved; the trend in stage IIIB and IVA1 was worse but did not reach statistical significance, whereas OS for stage IV disease was significantly worse (48 months for stage IVA and 33 months for stage IVB).

In univariable analyses, six of 10 variables tested were significantly associated with a worse survival. These included stage IV, age greater than 60 years, absent FT in skin, LCT in skin, elevated WBC, and elevated LDH (Table 2). An identical clone in skin and blood was associated with a trend toward a worse survival ($P = .086$).

Older age has previously been suggested to be associated with a worse survival in advanced MF/SS.[7,9,10] The mean age of this cohort was 63 years and was similar across stages. Both age greater than 60 years and greater than 70 years were independent adverse prognostic markers. Older patients may have compromised OS as a result of multiple factors including comorbidities and more limited treatment

Table 3. Median Survival and Predicted 1-, 2-, and 5-Year OS Rates According to Stage of MF/SS

		OS							DSS						
						Rate (%)							Rate (%)		
Stage	No. of Patients	Median (months)	95% CI (months)	IQR (months)	RM (months)	1 Year	2 Years	5 Years	Median (months)	95% CI (months)	IQR (months)	RM (months)	1 Year	2 Years	5 Years
IIB	457	68.37	61.18 to NR	31.0-NR	59.5	88.50	80.10	57.40	NR	NA	42.2-NR	66.5	93.10	86.40	67.47
III (all)*	320	NR	57.76 to NR	36.8-NR	60.9	89.50	79.50	58.20	NR	NA	43.9-NR	65.9	91.77	84.56	66.28
IIIA	187	NR	57.8 to NR	35.2-NR	61.7	89.60	79.80	60.20	NR	NA	43.9-NR	66.5	91.95	83..89	68.26
IIIB	119	62.4	44.8 to NR	32.8-NR	58.2	88.50	77.80	55.70	NR	NA	44.8-NR	65.4	93.22	86.77	66.12
IVA (all)†	463	47.5	43.0 to 56.10	22.3-NR	50.9	87.60	73.20	42.90	63.4	49.8 to NR	28.4-NR	57.3	91.63	80.03	52.34
IVA1	290	52.7	48.58 to 78.77	31.5-NR	55.7	90.40	79.40	48.30	66.2	50.9 to NR	38.5-NR	60.8	93.41	85.39	55.98
IVA2	127	29	23.7 to 44.4	13.6-68.7	40.4	81.00	59.60	32.90	44.4	27.2 to NR	20.1-NR	48.9	87.27	69.20	44.36
IVB	35	33.3	15.91 to NR	14.0-NR	42.5	78.50	54.30	39.00	33.3	15.9 to NR	4.0-NR	44.1	78.54	54.28	39.04
All stages	1,275	63	55.67 to 69.0	25.4-NR	56.3	88.10	76.60	51.90	NR	68.0 to NR	34.7-NR	62.6	91.79	82.59	61.03

Abbreviations: DSS, disease-specific survival; IQR, interquartile range; MF, mycosis fungoides; NR, not reached; OS, overall survival; RM, restricted mean; SS, Sézary syndrome.
*For 14 patients, data were not available to determine whether stage was IIIA or IIIB.
†For 46 patients, data were not available to determine whether stage was IVA1 or IVA2.

options. Treatments were not collected in this cohort, and their influence on outcome cannot be ascertained.

This cohort showed a male predominance, with a male-to-female ratio of 1.7:1, which is similar to previous reports,[3,5,7] but no difference in survival was shown between sexes. Male sex has been associated with a worse prognosis in some studies[7] but is not a consistent finding.[3,5,9,15]

Histologic features of FT, LCT, CD30 positivity, and a high proliferation index may be associated with aggressive disease. FT is reported when atypical lymphocytes are invading the follicular epithelium. Absent FT may result if the biopsy does not contain a follicle. Data completeness for FT and LCT was robust (> 80%), which reflects the ability to record these features on hematoxylin and eosin–stained slides. FT has been associated with treatment resistance and worse survival often in the context of early-stage disease. Among patients with stage IB disease who have FT, survival outcome is similar to patients with stage IIB disease, and FT may confer a worse prognosis in patients with LCT.[5,7,16-19] Conversely, in this advanced data set, the presence of FT was associated with a better prognosis in univariable analysis. However, FT was strongly associated with stage IIB disease and a younger age (median age, 59 years *v* 65 years without FT), and both confer a better prognosis. Moreover, FT was not significant in multivariable analysis. Other possibilities include that FT is a marker for progression from stage IB disease to advanced disease or that therapies in early-stage disease fail to treat FT disease, allowing progression, whereas patients with advanced disease with FT have systemic therapies capable of treating deep follicular disease. Alternatively, in early disease, the lack of highly relevant poor prognostic variables found in advanced disease such as elevated LDH and LCT makes FT significant. Benton et al[12] similarly found FT to be a strong predictor of poor survival in early-stage but not late-stage patients. Another explanation is that because FT is a skin-only marker, when one takes into account extracutaneous disease, adverse outcome of stage IV trumps any risk factor in skin. Further prospective studies of FT may determine whether this feature is relevant to survival or treatment response or is a predictor of progression in those with early-stage disease.

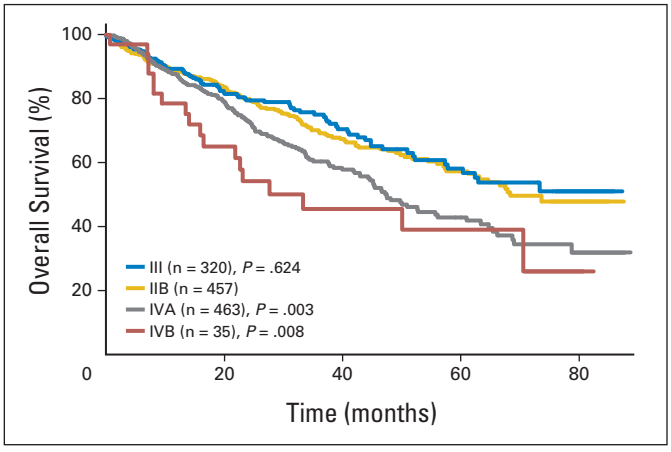

Fig 1. Kaplan-Meier plot showing survival by stage.

LCT in skin was an independent poor prognostic marker in this cohort, confirming earlier studies,[5,8,9,20] and remained significant in patients with skin tumors and erythroderma. The definition of LCT of more than 25% of atypical lymphocytes or clusters of cells having a diameter of more than four times that of normal lymphocytes has been widely accepted.[13] This definition allows comparisons between sites, and LCT is likely of prognostic importance. Further studies of LCT occurring at the time of disease progression and in extracutaneous sites such as lymph nodes will be informative.

CD30 and Ki-67 require special stains, and data completeness was 50% and 37%, respectively. Incomplete data (both not recorded and not done) may add bias because more thorough investigations may be associated with aggressive disease. Furthermore, the protocol stipulated that CD30 and Ki-67 should be recorded as absolute percentages (0% to 100%), but many centers had only recorded ranges. Unlike LCT, CD30 positivity has no standard definition, and variable reporting may account for conflicting reports in the literature.[5,9,21] We scored CD30 as positive if more than 10% of tumoral cells stained positively. Although we found a worse OS in $CD30^+$ patients, this was not statistically significant for the whole cohort but was associated with a worse OS in those with skin tumors (T3; $P < .001$).

Table 4. Prognostic Index Model Using Four Risk Factors (stage IV, age > 60 years, elevated LDH, and LCT in skin)

Risk of Poor Survival	No. of Patients	No. of Deaths	Stage (No. of patients) IIB	III	IV	1-Year Survival (months)	2-Year Survival (months)	5-Year Survival (months)	Median OS (months)	Hazard Ratio	95% CI	*P*
Low (0-1 risk factor)	327	100	166	134	27	94.0	86.6	67.8	NR	1		
Intermediate (2 risk factors)	329	123	91	82	156	83.9	71.9	43.5	46.4	2.09	1.56 to 2.80	< .001
High (3-4 risk factors)	201	100	20	4	177	84.7	62.2	27.6	34.2	2.91	2.15 to 3.96	< .001

Abbreviations: LCT, large-cell transformation; LDH, lactate dehydrogenase; NR, not reached; OS, overall survival.

Ki-67 protein reflects tumor cell proliferation, and a higher growth fraction is associated with a worse prognosis in multiple cancers. In our data set, we used a threshold value of 20% Ki-67–positive cells. No significance in OS was demonstrated for those with a low or high Ki-67 in the cohort as a whole, but as with $CD30^+$, high Ki-67 was associated with a significantly worse OS in those with skin tumors (T3; $P = .04$). Standardized histologic assessment will be required to determine whether any of these pathologic features are relevant prognostically.

Blood involvement characterizes SS but may also be seen at lower levels in classical MF. We found a trend toward a worse survival with increasing blood involvement, as reflected in OS times in stage IIIA, IIIB, and IVA1 disease (Appendix Fig A1). Similarly, total ALC is, at times, used to track peripheral-blood tumor burden. Both elevated and low ALCs seemed to carry a worse survival than ALC in the normal range, but neither reached statistical significance. ALCs greater than 10×10^9/L may have a poorer prognosis.[22,23] This study confirmed that patients with counts greater than 10×10^9/L had a worse prognosis, but this did not reach statistical significance ($P = .066$). Elevated WBC, which partially reflects ALC, was significantly associated with a worse prognosis compared with normal (or low) WBC in univariable but not multivariable analysis. Other factors that affect WBC, such as the eosinophil count, have been associated with a worse prognosis in SS[24] and may be relevant to study in future trials.

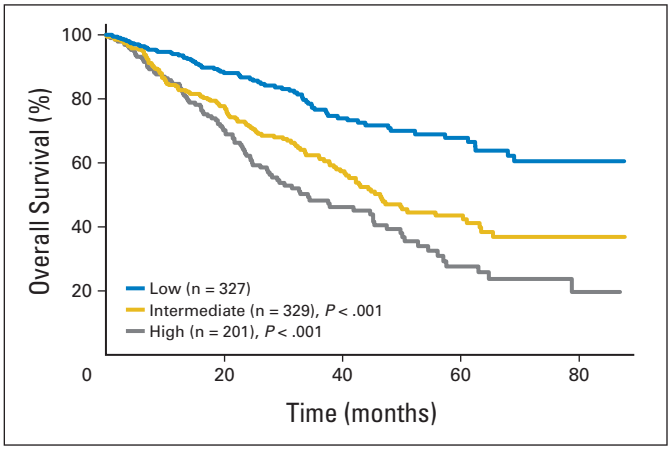

Fig 2. Kaplan-Meier plot showing prognostic index model for low-, intermediate-, and high-risk groups. Variables included in the prognostic index model were stage IV, elevated lactate dehydrogenase, age greater than 60 years, and large-cell transformation in skin (low risk = zero to one variable; intermediate risk = two variables; high risk = three to four variables).

The presence of an identical clone in skin and blood clone is classified as a (no clone) or b (clone) alongside blood (B) classification. The presence of a blood clone does not currently alter stage but provides a means of recording low-level blood involvement. An identical blood clone was detected in 49% of patients in this advanced cohort and was associated with a trend toward a worse survival, with median survival time of 49.8 months ($P = .086$). An identical blood clone has been associated with a worse outcome in early-stage MF but may not be relevant in advanced disease where tumor burden is already greater.

Forty-nine percent of this cohort had elevated LDH, which was an independent poor prognostic marker for OS ($P = .002$). Elevated LDH is associated with a worse survival in a number of lymphomas and is used in prognostic indices for aggressive follicular and mantle-cell lymphomas.[25-27]

Prognostic indices may be developed to stratify patients according to survival by combining prognostic factors. A prognostic index must be simple and reproducible. Prognostic indices are useful when there is a wide range of survival between stages and a variety of prognostic variables. MF/SS fits this characterization. Furthermore treatment in MF/SS is frequently decided on an individual patient basis with consideration of prognostic factors beyond stage. Four variables (stage IV, age > 60 years, elevated LDH, and LCT in skin) were independently prognostic for survival in this study. Using these four variables in a prognostic index model, we identified the following three risk groups with significantly different survival: low risk (zero to one variable), intermediate risk (two variables), and high risk (three to four variables), with 5-year predicted OS rates of 67.8%, 43.5%, and 27.6%, respectively (Table 4, Fig 2). Benton et al[12] recently reported separate cutaneous lymphoma prognostic indices for early-stage (IA to IIA) and advanced-stage (IIB to IVB) MF/SS. The advanced-stage index was developed using retrospective data but included a much smaller number of advanced-stage patients (derivation set, n = 445). Age greater than 60 years was also identified as a significant adverse prognostic factor in the late-stage model. Male sex carried a poorer survival but was not found to be important in our data set ($P = .93$). The other factors included in this index were related to stage (N2/3, B1/2, and M1). A lack of full data on LDH precluded inclusion.

This study of advanced stages of MF/SS confirms stage IV as a poor prognostic stage and identifies increasing age, elevated LDH, and LCT in the skin as independent poor prognostic markers that may be used together in a prognostic model to identify three risk groups across stages with significantly different survival (Table 4, Fig 2). This retrospective study has proven the ability of these international centers to work together, but the accuracy or consistency of data entry relating

to the interpretation of pathology reports cannot be confirmed because no quality assessment of data entry was performed. A prospective study with consensus criteria, consistently collected data, central pathologic review, and data monitoring is planned by CLIC to test these parameters with others and further refine and validate this prognostic index in advanced MF/SS.

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Disclosures provided by the authors are available with this article at www.jco.org.

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Cutaneous Lymphoma International Consortium Study of Outcome in Advanced Stages of Mycosis Fungoides and Sézary Syndrome: Effect of Specific Prognostic Markers on Survival and Development of a Prognostic Model

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Appendix

Table A1. ISCL/EORTC Revised Staging System for MF/SS

Stage	T*	N†	M‡	B§
IA	1	0	0	0, 1
IB	2	0	0	0, 1
IIA	1, 2	1, 2	0	0, 1
IIB	3	0-2	0	0, 1
IIIA	4	0-2	0	0
IIIB	4	0-2	0	1
IVA1	1-4	0-2	0	2
IVA2	1-4	3	0	0-2
IVB	1-4	0-3	1	0-2

Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; ISCL, International Society for Cutaneous Lymphomas; MF, mycosis fungoides; SS, Sézary syndrome.

*T1, patches or plaques covering < 10% of the body surface. Further stratified into T1a (patches only) and T1b (plaque ± patch); T2, patches or plaques ≥ 10% of the body surface. Further stratified into T2a (patches only) and T2b (plaque ± patch); T3, more than one tumor (≥ 1 cm); T4, erythroderma, which means involvement of more than 80% of skin.

†B0, absence of significant blood involvement: < 5% of peripheral-blood lymphocytes are atypical (Sézary) cells; B0a, clone negative; B0b, clone positive. B1, low blood tumor burden: > 5% of peripheral-blood lymphocytes are atypical (Sézary) cells but does not meet the criteria of B2; B1a, clone negative; B1b, clone positive. B2, high blood tumor burden: > 1,000/L Sézary cells with positive clone.

‡N0, no palpable lymphadenopathy or histologic evidence of mycosis fungoides. N1, clinically abnormal peripheral lymph nodes and histopathology Dutch grade 1 or National Cancer Institute (NCI) LN0-2. Further stratified into N1a (clone negative) and Nab (clone positive). N2, clinically abnormal peripheral lymph nodes and histopathology Dutch grade 2 or NCI LN3. Further stratified into N2a (clone negative) and N2b (clone positive). N3, clinically abnormal peripheral lymph nodes and histopathology Dutch grade 3 or 4 or NCI LN4 (clone positive or negative). Nx, clinically abnormal peripheral lymph nodes but no histologic confirmation.

§M0, no visceral involvement; M1, histologically confirmed visceral involvement.

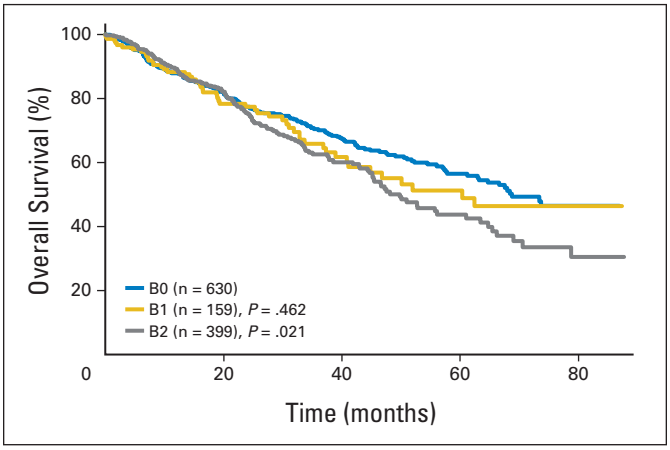

Fig A1. Kaplan-Meier plot showing survival according to blood (B) classification.

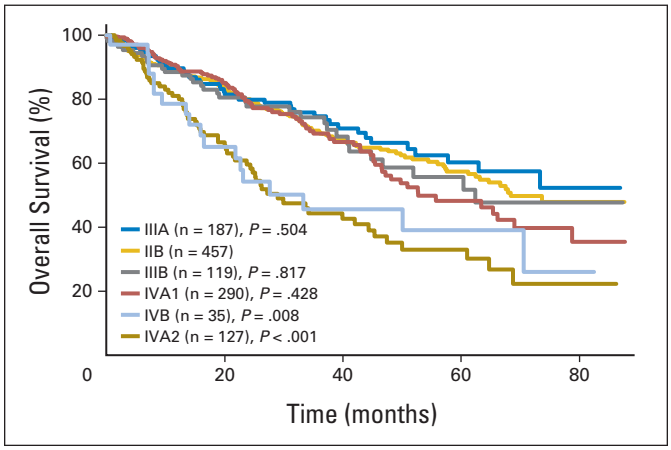

Fig A2. Kaplan-Meier plot showing survival by revised staging.