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SYSTEMATIC REVIEW

Quality of life in patients with Mycosis Fungoides and Sézary Syndrome: a systematic review of the literature

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Abstract

Cutaneous T-cell Lymphoma's (CTCL) are a rare, heterogeneous group of T-cell lymphomas that primarily manifest in the skin. Mycosis fungoides (MF) and Sézary syndrome (SS) are considered the classic types of CTCL. The diverse manifestation of CTCL results in a wide range of symptoms with a possible mild to severe impact on Quality of Life (QoL) depending on the disease stage. Previous studies on QoL in CTCL patients report diverse patient populations and use many different QoL instruments. In the current literature, a clear overview on the influence of the different stages of disease (early MF, late-stage MF/SS or total group) on the QoL is lacking. Therefore, a systematic search of the literature was conducted using the PubMed, Embase, PsycINFO and Web of Science databases. Studies were included if they described QoL in patients with MF and SS retrieved by standardized instruments or qualitative interviews. In total, 24 studies were included using 18 different questionnaires to report on dermatology-specific, cancer-specific and generic QoL. The effect on QoL was found to be greater in patients with late-stage disease as compared to early stage disease, with significant impairments on functional, emotional and physical domains. Nonetheless, even in patients with limited disease, QoL was mildly to moderately affected. Overall, pruritus was the most frequent reported and most bothersome symptom. Significant influence of the disease on daily life activities were found, not only in patients but also on caregivers and family. This broad, structured overview on QoL in MF and SS patients underlines the influence of disease stage on QoL, and therefore, recommends future studies to distinguish between disease stages when reporting results. Furthermore, this overview can inform clinicians in clinical practice by creating awareness of QoL deficits according to disease stage.

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Conflicts of interest

R. Willemze: Participation on a Data Safety Monitoring Board or Advisory Board; Helsinn Healthcare S.A. M.H. Vermeer: Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events and Participation on a Data Safety Monitoring Board or Advisory Board; Kyowa. No conflicts of interest to declare for authors R. Ottevanger, S. van Beugen, A.W.M. Evers and K. D. Quint

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Introduction

Primary cutaneous lymphomas are a heterogeneous group of T- and B-cell lymphomas that manifest in the skin with no evidence of extracutaneous disease at the time of diagnosis.[1,2] Mycosis fungoides (MF) and Sézary syndrome (SS) are considered the classic types of Cutaneous T-cell Lymphoma (CTCL). The most common subtype is MF and accounts for 60% of CTCLs. The different disease stages of MF vary from only localized patches and plaques to ulcerative tumours and/or erythrodermic patients with extracutaneous involvement.[3] SS is a rare aggressive leukemic type of CTCL with an estimated incidence of 0.075 per 100 000 persons, defined by the triad of erythroderma, lymphadenopathy and blood involvement.[2,4]

The diverse manifestation of CTCL results in a wide range of symptoms from mild to very severe. Frequently reported symptoms are pain, itching, scaling and skin redness. Cutaneous lymphomas can, therefore, have a profound and severe impact on experienced Quality of Life (QoL) with regards to functioning, emotional- and social well-being, with a high percentage of

patients suffering from anxiety and high depression levels compared to healthy individuals.[5,6]

Instruments to report on QoL in CTCL patients include a mix of general and dermatology-specific QoL questionnaires and qualitative interviews.[7] Previous studies on QoL in CTCL patients report diverse patient populations and use many different QoL instruments. Recent reviews of the clinical management and burden of disease of CTCL have briefly highlighted the impact of CTCL on QoL.[7–9] However, in the current literature a clear overview on the influence of QoL in the different stages of disease (early MF, late-stage MF/SS or total group) is lacking. Therefore, a practical overview can inform treating physicians in clinical practice by creating awareness of QoL deficits according to disease stage. This review aimed to provide a clear overview on the effects of the different clinical stages of CTCL (MF and SS) on (skin related) quality of life.

Methods

Literature search strategy and study selection

A systematic search of the literature was conducted for this review using the computerized bibliographic databases PubMed, Embase, PsycINFO and Web of Science. All databases were searched for English articles published from January 1, 2000 until July 6, 2020. The search procedure was conducted and documented according to PRISMA guidelines for systematic reviews.[10] The search included keywords related to 'cutaneous T-cell lymphoma', 'Mycosis fungoides', 'Folliculotropic mycosis fungoides', 'Sézary syndrome' and 'quality of life'. The detailed search strings are outlined in Supplementary material.

Inclusion and exclusion criteria

We included only original articles that fulfilled our inclusion criteria. Studies were included if they described the quality of life in patients with MF and/or SS retrieved by questionnaires or qualitative interviews. In case of studies describing the effect of an intervention, only the QoL data at baseline were included in the results. If study populations involved less than 15% of patients with other types of CTCL, these data were also included. Studies with <5 patients, patients aged <18 years, reviews, letters and comments without aggregated data were excluded.

Data collection process

Titles and abstracts of retrieved articles were independently screened by two authors (RO and KQ) for inclusion criteria. If there was disagreement between the two authors, the opinion of a third author was decisive (MV). Subsequently, the full text of potentially relevant articles were assessed for eligibility by the same two authors. After the full text screening, the references of the included studies were manually screened for additional eligible articles.

QoL data were reported for several stages of CTCL if possible; early stage MF (stage IA-IIA), late-stage MF (stage IIB-IVB), SS and mixed stages MF/SS.

In case of a mix of CTCL stages, undefined stages of disease or in case that no separate QoL results were reported per disease stage, the results of that particular study were reported under mixed stages MF/SS.

The following study characteristics were extracted from the included studies: year of publication, country, sample size, age of population, CTCL diagnosis, disease stage and reported CTCL stages. The reported QoL measurements were extracted from (validated) questionnaires and qualitative interviews. In addition, if studies also described other outcomes, such as severity of pruritis, depression, anxiety and illness perception, this was also extracted and correlated to the measured QoL from questionnaires. Furthermore, if included studies compared QoL results to other diseases or general population, these were also reported separately.

No formal meta-analysis with pooling of results was performed, as it was expected that the included studies would have a high degree of heterogeneity of study populations with regards to staging and extent of disease, prior and current therapies, and varying points of time of conducting the outcome measurements. Due to the lack of homogenic data, this was of no additional value.

Results

Methodological results

A total of 317 studies were found and screened for eligibility. Details of the selection process for eligible studies are shown in Figure 1. In total, 24 studies matched the eligibility criteria.[5,6,11–32] All included studies were published between 2001 and 2020. The sample size ranged from 5 to 630. In total, 21 studies used QoL questionnaires and four studies used qualitative interviews.[5,6,11–32] Of these studies, one study used both QoL questionnaires and qualitative interviews.[31]

QoL instruments

A total of 18 different questionnaires were used to report on QoL. These concerned dermatology-specific, cancer-specific and generic QoL instruments. Furthermore, specific pruritus instruments were used in 7 of the included studies. A brief description of the used instruments is provided below and a complete overview of the used instruments per study is displayed in Table 1.

Dermatology-specific QoL instruments

Skindex The Skindex was used in 9 of 24 publications; 7 of these used the Skindex-29 and two studies used a shortened version, the Skindex-16.[33,34] Individual questions measure the frequency on three domains; symptoms, emotions and functional

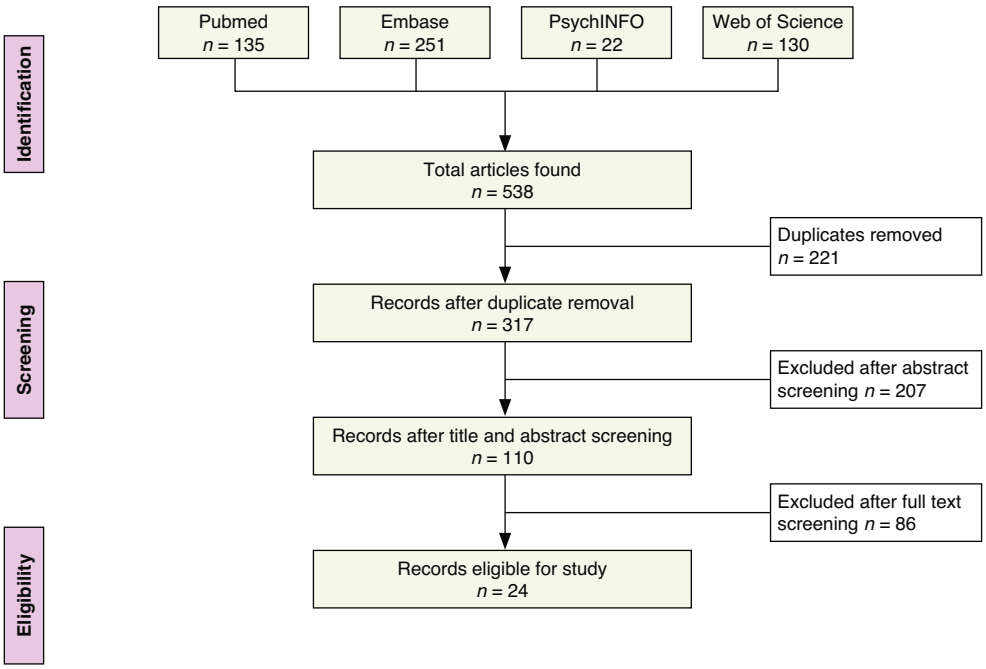

Figure 1 Prisma Flowchart of systematic review of the literature.

limitations, by using 5-point scales ranging from 1 ('never') to 5 ('all the time'). Prinsen et al. have established cut-off scores for the individual domains.[35] These are ≥39, ≥42 and ≥52 for mild, moderately, and severely impaired for the symptoms domain, ≥24, ≥35 and ≥39 for emotions domain, and ≥21, ≥32 and ≥37 for the functional limitation domain, respectively. The cut-off score for the total Skindex-29 score is ≥25 for mild, ≥32 for moderate and ≥44 for severe impairment.[35]

Dermatology Life Quality Index (DLQI) The DLQI was used to assess QoL in 3 from the 24 studies. The score ranges from 0 (no impairment) to 30 (maximum impairment). There are 5 categories in the DLQI based on the sumscore; 0-1 no effect on QoL, 2-5 small effect, 6-10 moderate effect, 11-20 very large effect and 21-30 extremely large effect on QoL.[36,37]

Cancer-specific questionnaires

The Functional Assessment of Cancer Therapy – General (FACT-G) The FACT-G is used in three studies to assess the quality of life in cancer patient populations.[38–40] It is a self-administered, 27-item questionnaire that assesses five Health Related Quality of Life (HRQoL) domains; physical well-being, social and/or family well-being, emotional- and functional well-being. The domains are rated on a 5-point Likert scale from 0 ('not at all') to 4 ('very much'). The total score ranges from 0 to 108, with higher scores correlating with higher HRQoL. Cut-off scores for impairment have not been established.[38]

Spitzer The Spitzer questionnaire is a 5-item QoL questionnaire developed for cancer patients with a score of 0 representing 'worst' and 40 'best' and was used in one study.[41]

Core quality of life questionnaire (QLQ-C30) The QLQ-C30 evaluates the HRQoL in international clinical trials in oncology patients in a 9-item questionnaire.[42] It includes subscales that assess the global health status, physical functioning, social functioning, emotional functioning, cognitive functioning, role functioning, symptoms and financial impact. No overall total score or clinical related categories exist. The global health status ranges from 0 (low) to 100 (healthy level of functioning). It was used in two studies.

Generic QoL instruments

Short form health survey (SF-36) The SF-36 is a 36-item generic QoL instrument that measures the impact of disease in eight different domains; physical- and role functioning, bodily pain, general health perception, energy/vitality, social functioning, role functioning and general mental health.[43] Domain scores range

Table 1 Study characteristics of included studies

Author	Year	Country	*n*	Age (mean or median)	Diagnosis	Stage	Reported stage	Skin Specific QoL	Generic QoL	Cancer-specific QoL	Pruritus	Other
Quantitative												
Ayyalaraju et al[10]	2003	UK, USA	51	*	MF	Hospitalized	Mixed	DLQI				
Booken et al[11]	2011	Germany	5	μ 61 (51–68)	SS/erythrodermic MF	MF IIIB, SS IVA	Late	DLQI			VAS	
Bouwhuis et al[12]	2003	USA	20	*	SS		Late		SF-36			
Demierre et al[13]	2007	USA	11	M 62 (39–80)	MF/SS	IB-IV	Mixed	SD-29		FG-V4		
Demierre et al[5]	2006	USA	630	M 57	MF/SS	IA-IV	Mixed					Self-made
Demierre et al[14]	2005	USA	22	μ 63.1 (32–81)	MF	I-IIA, II-IVB	Early and late	SD-29		FG-V4		
Duvic et al[15]	2001	USA	94	M 64 (27–89)	CTCL	IIB-IVB	Late			Spitzer		
Duvic et al[16]	2002	USA	71	μ 61	MF/SS	IB-III	Mixed			FG-V3	VAS	
Engin et al[6]	2020	Turkey	52	μ 46	MF	IA-IVB	Mixed		SF-36			BDI, BAI
Herbosa et al[17]	2020	USA	115	M Early stage 64.2 (59.2–72.2)	MF/SS	IIB-IVB	Early and	SD-29	SF-36, HUI-3		VAS	
				M Late stage 67.1 (47.0–71.9)			late				5D	
Holahan et al[18]	2018	USA	105	μ 61.07	MF/SS	I–IV	Mixed	SD-16	EQ5D			
Illidge et al[19]	2013	UK	36	M 65 (38–83)	MF	IB-IVA	Mixed	SD-29		qlq-c30	VAS	
Jennings et al[20]	2019	USA	8	(37–81)	MF	*	Mixed	DLQI			VAS	
Molloy et al[21]	2020	Multinational	238	M 60 (49-70)	MF/SS	IA-IVB	Mixed	SD-29				
Porkert et al[22]	2018	Austria	55	μ 63.8(±13.27)	CTCL	IA-IIA, IIB-IVB	Early and late	SD-29				IPQ-R
Quaglino et al[23]	2020	Multinational	56	M 57 (5–97)	MF	IA-IIA	Early	SD-29				
Sampogna et al[24]	2009	Italy	95	μ 56 (±18)	MF/SS	IA-III	Early, late, and mixed	SD-29		qlq-c30		
Semenov et al[25]	2020	USA	67	μ 65 (±12.8)	MF/SS	IA-IVB	Early and late		HUI-3			
Steinke et al[26]	2018	Multinational	15	μ 51.1 (± 18.2)	MF/SS	*	Mixed	DLQI			NRS	
											Itchy-QoL	
Wright et al[27]	2013	UK	100	μ 57.9 (± 12.9)	MF/SS	I-IV	Early, late, and mixed	SD-29			VAS	
Qualitative												
Beynon et al[28]	2015	UK	19	41-83	CTCL	IAB, IIB, III, IVA	Mixed					Semi-structured
Bhat et al [29]	2020	USA	18	M 62 (IQR18)	MF/SS	IIB-IV	Early					Interview
Demierre et al[30]	2011	UK, USA	19	M 64 (25–80)	MF/SS	IA-IVA	Mixed	SD-16				Interview
Selman et al[31]	2015	UK	14	36–85	MF/SS	IB-IVB	Mixed					Semi-structured

n, number of patients; *, missing; ±, SD; (), range; μ, mean; M, median; MF, Mycosis fungoides; SS, Sézary syndrome; DLQI, Dermatology Life Quality Index; SD-29/16, Skindex-29/16; SF-36, Shoft Form Health Survey, HUI-3, Health Utility Index; EQ5D, EuroQoL-5D; FG-V4/3, Functional Assessment of Cancer Therapy – General Version 4/3; QLQ-C30, Core Quality of Life questionnaire; VAS, Visual Analoge Score; 5D, Pruritus-5D itch scale; Itchy-QoL, Itchy Quality of Life; BDI, Back Depression Inventory; BAI, Beck Anxiety Inventory; IPQ-R, Revised Illness Perception Questionnaire.

from 0 to 100, with higher scores correlating with a better health status, with a score difference of 3–5 points being considered clinically meaningful.[44] The SF-36 was reported in three studies.

Health utility index (HUI-3) The HUI-3 is also a widely used instrument that assesses overall QoL by a health utility score and was used in two studies. It consists of 15 questions that result in a utility score ranging from −0.36 ('worse than death') to 1 ('perfect health'). The sum scores are not related to a clinical category other than that a composite score of less than 0.70 indicates severe disability.[45]

EuroQoL-5D (EQ5D) The EQ5D includes six items and measures generic HRQoL with regards to mobility, self-care, usual activities, pain/discomfort and anxiety/depression.[46] It also includes a Visual Analogue Scale (VAS) that rates patients their health status between 0 ('worst health') and 100 ('best health'). It was used in one study.

Generic instruments for specific symptoms and illness perceptions

Pruritus A VAS and Numeric Rating Score (NRS) were used to measure the severity of pruritus on a scale ranging from 0 (none) to 10 (worst imaginable).[47] A 5D pruritus assessment was used in one study to assess pruritus over the past two weeks along five domains: degree, duration, direction (improvement or worsening), disability and distribution resulting in a composite score ranging from 5 (no pruritus) to 25 (most severe pruritus).[48] Furthermore, the Itchy-QoL was used in one study as a pruritus-specific QoL instrument that addresses symptoms, functional limitations and emotions. The overall score consists of the average of the responses to all the items ranging from 22 to 110.[49]

Depression, anxiety and illness perception Two questionnaires were used that addressed the level of depression (Beck Depression Inventory (BDI)) or anxiety (Beck Anxiety Inventory (BAI)) for patients with CTCL.[50,51] The BDI is a 21-question instrument that value responses between 0 and 3 with a score between 0 and 13 correlating with minimal depression, 14–19 with mild depression, 20–28 with moderate and 29–63 indicating severe depression.[51] BAI also is a 21-item questionnaire with a similar scoring system, but addresses anxiety instead of depression.[50] The Revised Illness Perception Questionnaire (IPQ-R) was used to assess illness perception in term of one's personal beliefs about the disease.[52]

Qualitative studies

Qualitative studies were included in order to report QoL related outcomes that were not addressed in the standardized QoL instruments. In case, both qualitative outcomes and standardized QoL instruments were assessed, the results of both methods were reported.

Quality of life results

Disease specific results: QoL in MF and SS In the 24 included studies in this review, QoL was reported for heterogeneous study populations with various stages of the disease and differences in prior- and current therapies.[5,6,11–32] The vast majority of studies described study populations that featured stage MF IA-IVB and SS and did not report separate results for early and late-stage disease (Table 1). The common domains that were addressed regarding QoL were related to symptoms, emotional/psychological and functional domains and general health status. All studies describe a significant negative impact on patient's QoL with most studies focussing on more advanced stages of the disease (Tables 2–5).

Early stage disease

The great diversity in severity of the disease was also reflected by the degree of affected QoL across the various stages of the

Table 2 Skindex scores for the included studies per domain

Skindex-29	Domain scores			
Study	**Symptoms**	**Emotions**	**Functional**	**Total**
Demierre et al. (2007)	21 (±4)	27 (±10)	26 (±9)	75 (±23)
Demierre et al. (2005)	19 (±72)	24 (±9)	24 (±10)	67 (±24)
Early stage	15 (±7)	18 (±7)	18 (±8)	51 (±18)
Late stage	22 (±6)	29 (±7)	29 (±10)	80 (±21)
Herbosa et al. (2020)				
Early stage	32 (±24)	30 (±23)	18 (±24)	-
Late stage	56 (±19)	54 (±27)	44 (±32)	-
Illidge et al. (2013)	68 [57-79]	55 [43-75]	55 [31-71]	-
Molloy et al. (2019)	39 [21-57]	35 [20-55]	13 [4-34]	30 [15-47]
Porkert et al. (2018)				
Early stage	32 (±18)	32 (±21)	18 (±19)	84 (±52.4)
Late stage	45(±18)	46 (±30)	33 (±23)	124 (±63)
Quaglino et al. (2020)	-	-	-	24 (95% CI 18-30)
Wright et al. (2013)	11 (±7)	16 (±10)	16 (±13)	43 (±28)
Early stage	10 (±6)	15 (±10)	13 (±13)	39 (±27)
Late stage	13 (±7)	18 (±11)	20 (±13)	51 (±28)
Skindex-16				
Holahan et al. (2018)	2.1 (±1.9)	1.09 (±1.6)	1.5 (±1.5)	25.7 (±25.6)

Number are displayed as mean (± standard deviation), median [interquartile range P25-P75] or mean (corresponding 95% confidence interval).

Table 3 Pruritis scores related to the skin specific, generic and cancer related QoL

Study	VAS/NRS (μ/M)	Pruritus related QoI	QoL Skin specific	Generic	Cancer-specific
Booken et al (2011) Late stage	μ 9.8 (±0.4)		DLQI: 20.4 (±5.2)		
Duvic et al. (2002) Mixed stage	M 5.4				FACT-G Functional: 17 Physical: 23 Emotional: 16 Social: 21 Total: 81
Herbosa et al. (2020)					
Early stage	μ 3.3 (±3.0)	5D-pruritis: 10.7 (±5.2)	Skindex-29 Symptoms: 32(±24) Emotions: 30(±23) Functional: 18 (±24)	HUI-3: 0.69 (±0.3)	
Late stage	μ 6.1 (±2.9)	5D-puritus: 16.6 (±5.4)	Skindex-29 Symptoms: 56 (±19) Emotions: 54 (±27) Functional: 44 (±32)	HUI-3: 0.51 (±0.33)	
Illidge et al. (2013) Mixed stage	M 7.5 [6.5-9.5]		Skindex-29 Symptoms: 68 [57-79] Emotions: 55 [43-75] Functional: 55 [31-71]		QLQ Global health status: 50 [33-67]
Jennings et al. (2019) Mixed stage	M 3.4 (±3.4)		DLQI: 3 [1-10]		
Steinke et al. (2018) Mixed stage	*μ 5.3 (±3.2)*	Itchy-QoL 60.5 (±22.3)	DLQI: 12.1 (±8.3)		
Wright et al. (2013) Mixed stage	μ 3.2 (±3.2)		Skindex-29 Symptoms: 11 (±7) Emotions: 16 (±10) Functional: 16 (±13) Total: 43 (±28)		
Early stage	μ 2.8 (±3.1)		Skindex-29 Symptoms: 10 (±6) Emotions: 15 (±10) Functional: 13 (±13) Total: 39 (±27)		
Late stage	μ 3.9 (±3.1)		Skindex-29 Symptoms: 13 (±7) Emotions: 18 (±11) Functional: 20 (±13) Total: 51 (±18)		

Number are displayed as mean (± standard deviation) or median [interquartile range P25-P75]; *Italic*: NRS

disease. Although it was found that even in patients with a limited disease (early stage MF), the QoL was significantly affected.[18,23,24,28]

Dermatology-specific QoL Five studies reported separate results with regards to early MF with the Skindex-29 and one study reported on the Skindex-16 (Table 2).[15,18,23,24,28,31] According to Demierre et al. (2011) and Samponga et al. itching was the most frequent reported symptom.[25,31] The degree of QoL impairment varied greatly. Quaglino et al. reported that 31% of their 56 patients had moderate- and 20% had severe impairment on QoL due to early MF.[24] Four other studies reported less impact on the three domains of the Skindex-29 with average scores ranging in the mild-moderately affected categories.[15,18,23,28]

Generic QoL Not only dermatology-specific but also general QoL was affected in early stage MF. HUI-3 scores near the threshold of severe disability (<0.70) of 0.72 were reported by Semenov et al.[26] Herbosa et al. also found an average HUI-3 score of 0.69 (±0.3), which indicated severe disability and SF-36 scores of 59 (±22) out of 100.[18] Early MF caused decrements in

Table 4 FACT-G scores of included studies and subscores for the 4 domains

FACT-G	V.	Domain scores				
Study		Functional	Physical	Emotional	Social	Total
Demierre et al. (2007)	4	19(±6)	25 (±3)	18(±5)	20 (±5)	81 (±18)
Demierre et al. (2005)	4	19 (±7)	23 (±6)	18 (±6)	22 (±5)	82 (±20)
Duvic et al. (2002)	3	17	23	16	21	81

Number are displayed as mean (± standard deviation) or median [interquartile range P25-P75]; V., version

social functioning, role limitation due to physical health and emotional problems.[18]

Cancer-specific Low numbers of patients with insomnia by the QLQ-C30 were found; 0% in MF IA and 4.3% in stage IB-IIA in the study of Sampogna et al. [25] Low scale scores were reported by Demiere et al. in all four FACT-G subscales (physical, social/family, emotional and functioning well-being), indicating impaired QoL.[15]

Generic instruments for specific symptoms and illness perceptions Pruritus was the most frequent reported symptom. Mean pruritus severity scores on a scale between 0 (none) and 10 (worst imaginable) for early stage disease were 2.4 and 3.3, respectively (Table 3).[18,28] Herbosa et al. also reported significant intensity of pruritus in early stage disease with a score of 10.7 (±5.2) on the 5D pruritus score (5; no pruritus to 25; most severe pruritus).[18]

With regards to management of the disease, Porkert et al.[23] found that patients with early stage MF had positive beliefs that the disease could be controlled by treatment and that they had a good understanding of the disease based on IPQ-R results.

Late-stage disease (MF/SS)

Late-stage disease was found to have a greater effect on the QoL than early stage disease.(15, 18, 22, 23, 25, 26, 28, 53; Table 2–5).

Dermatology-specific QoL Four studies reported separate results for the Skindex-29 (Table 2).[15,18,23,28] The scores in the three domains remained highly variable between studies.

Table 5 DLQI scores for the included studies

DLQI	Total
Study	
Ayyalaraju et al. (2003)	6.3 (±6.7)
Booken et al (2011)	20.4 (±5.2)
Jennings et al. (2019)	3 [1-10]
Steinke et al. y	12.1 (±8.3)

Number are displayed as mean (± standard deviation) or median [interquartile range P25-P75]

Herbosa et al. reported severe impairment with regards to the symptoms, emotions and functionality in the Skindex-29.[18] Porkert et al. also reported severe impairment on the emotional domain, but moderate impairment in the symptoms and functioning domains.[23] Demierre et al. (2005) and Wright et al. reported scores with lesser impact classified as mild impairment on the three QoL domains.[15,28]

Generic QoL General health status was also substantially lower in advanced stage than in early stage disease. With HUI-3 scores between 0.51 and 0.56, indicating severe disability, and SF-36 scores of 55 (±24) out of 100.[18,26]

Cancer-specific QoL FACT-G scores were also significantly lower in advanced disease stage than early stage (72 vs. 94, $p = 0.005$) in Demierre et al. (2005).[15] However, also relatively higher QoL scores were found with a Spitzer QoL score of 30 (range 11–40) indicating good general QoL.[16]

Generic instruments for specific symptoms and illness perceptions Pruritus was also the most frequently reported symptom. The intensity of the pruritus was reported to be moderate-severe with VAS/NRS scores of 3.9 (±3.1), 3.9 and 6.1 (±2.92) for late-stage disease.[17,18,28] A more advanced disease stage and more severe pruritus symptoms were associated with poorer QoL.[28]

Porkert et al. described that advanced stage disease patients associated more general symptoms with their disease and often report fluctuation of their symptoms. Furthermore, they associated their chronic disease course with negative consequences and experienced emotional distress with the belief that their illness could not be controlled personally or therapeutically.[23] Patients with stage IIB and III disease on average experienced insomnia in 30%, which was significantly higher than in early stage disease.[25]

Erythrodermic MF/SS

Only two studies reported separate results for patients with SS or erythrodermic MF (Table 1).[12,13] QoL was the most affected in this group of patients (Table 3 and 5).

Dermatology-specific QoL Booken et al. reported a very large effect on QoL based on a DLQI score of 20 (±5) in five patients

(Table 5).[12] Sexual impairment as rated by the Skindex-29 was seen in 27% of patients with SS.[25]

Generic QoL General health measured by SF-36 was also significantly affected with regards to physical functioning, low social functioning and vitality levels.[13]

Generic instruments for specific symptoms and illness perceptions Pruritus was prevalent with a very high VAS intensity score of 9.8 (±0.4).[12]

Mixed stages MF/SS

Twelve studies described cohorts of patients from stage IA-IVB/SS without reporting separate aggregated data per disease stage (Table 1).

Dermatology-specific QoL Molloy et al. reported Skindex-29 results of 283 patients of which 182 (64%) with early stage (Table 2).[22] In general, they found mild-moderate impairment for MF/SS with a median global score of 30, but the interquartile range was broad, 15–47. Patients with late-stage disease had worse overall HRQoL, more symptoms and functional impairment.[22] In addition, Demierre et al. (2007)[14] also found that the emotional scale was the most strongly related to stage in their study results. Higher disease stage correlated to worse outcomes.

Sampogna et al. found that higher impact on QoL was associated with a higher T-stage. The results for symptoms were 23, 42 and 47 for T1, T2 and T3, respectively.[25] Subgroup scores for emotions were 30, 37 and 52, and 18, 26 and 37 for functioning scales respectively. This indicates that T3-stage disease severely impairs QoL. No differences were observed in the different age groups.[25]

DLQI scores of 6.3 (±6.7), 3 [1–10]) and 12 (±8)) were reported by studies describing divers populations of MF, although these numbers do indicate a small to moderate effect on general QoL in contrast to other studies.[11,21,27]

Generic QoL The HRQoL measured with the EQ5D by Holahan et al. was 0.83 (±0.20), which correlated to a good health status.[19]

Cancer-specific QoL Duvic et al. (2002)[17] reported on 71 patients with MF and SS stage IB-IV. The composite FACT-G score was 80.6 (Table 4). Demierre et al.[14] also reported an overall FACT-G score of 81 (±18).

General health status was reported with regards to QLQ-C30 scores by Illidge et al., with their cohort scoring 50 [33–67] indicating a severe effect of MF/SS on health status.[20]

Generic instruments for specific symptoms and illness perceptions A prevalence of 88% of pruritus was reported in the study of Wright et al. of which 30% of patients reported that they had pruritus 'often' and 16% reporting that they had pruritus 'all the time'.[28]

VAS scores of 3.4 (±3.4), 5.3 (±2.5), 5.4 and 7.5 [6.5–9.5] were reported, with severity depending on the percentages of late-stage featuring the study groups, with advanced stage tending to have more severe pruritus.[17,20,21,27]

Demierre et al. reported QoL results of a self-made questionnaire in 630 patients with 80% self-reported early stage disease. 88% of the respondents reported itching and 54% pain. Tiredness was reported by 66% of the patients. Choice of clothes were influenced by disease symptoms in 63% of patients. The psychosocial impact was also high, with 94% reported worrying about the disease seriousness or death, 62% felt unattractive due to their disease and 47% had an affected sex-life.[5] Psychological symptoms were present in 34% of the patients in the study of Sampogna et al.[25]

Comparison to other diseases and general population

Multiple studies compared QoL scores of MF/SS with other dermatologic and non-dermatologic diseases.[6,13,19,22,25,26] As the QoL was very dependent on the degree of early- and late-stage disease, the comparison of QoL scores to other diseases also varied.

Patients with relatively mild disease had QoL scores comparable with psoriasis and vitiligo with regards to emotions and functioning, but experience more QoL impairment due to symptoms.[25] Molloy et al. and Holahan et al. also suggested that early stage MF is comparable with acne vulgaris, atopic dermatitis, contact dermatitis and psoriasis. SS is more severe with much higher scores than benign dermatoses and non-melanoma skin cancer.[19,22] However, Steinke et al. showed that dermatologic QoL in MF patients was more affected than in patients with atopic dermatitis, psoriasis and prurigo nodularis.[27]

Furthermore, compared to various other chronic conditions such as cancer or dermatitis, SS patients had a significantly lower mean physical component.[13] Overall, QoL measured with HUI-3 was lower in MF/SS than scores associated with patients with diabetes.[26]

General quality of life compared to healthy controls was significantly more affected in MF/SS.[6,13] Compared to a sex- and age-adjusted general population, patients with SS had lower general health, lower physical functioning, lower social functioning and lower vitality levels.[13]

Compared to a matched healthy control group the mean depression and anxiety scores for patients with MF/SS were significantly lower.[26]

Association between pruritus and QoL

There were seven studies that described dermatology-specific, generic or cancer-specific QoL, as well as the degree of pruritis (Table 3).[12,17,18,20,21,27,28] For early stage disease the skin specific QoL was relatively mildly affected, with pruritus scores of 3.3

(±3.0) and 2.8 (±3.1).[18,28] For late stage, the dermatology-specific and generic QoL was more severely affected and more intense pruritis were found. In the studies describing mixed stage disease, the pruritis scores seemed higher in the studies that described a lower QoL.[17,20,21,27,28] Steinke et al. reported that 42% of the patients indicated that their QoL was often or always affected because of itching. The itchy-QoL scores of MF indicated that the pruritus affected QoL was similar to that of atopic dermatitis and psoriaris vulgaris.[27]

Qualitative studies

Four studies reported results of a qualitative analysis based on (semi-structured) interviews in patients with early and advanced stage CTCL (Table 1).[29–32]

A recurrent theme was that a significant proportion of the patients felt that an earlier diagnosis might have reduced the spread of the disease. In the study of Bhat et al., 72% of patients reported that their skin disease was initially mistaken for psoriasis or eczema.[30,32] After the diagnosis was made, the rarity and lack of public understanding of the disease were frustrating to many patients.[30,31] Diagnosis could be shocking and frightening and there were descriptions of being 'devastated' or 'dumbfounded'. Furthermore, anxiety was associated with a diagnosis of cancer or a name that sounded like 'a fungus'.[29] Patients often had to correct or accommodate the misperception of their disease being contagious.[30]

Symptoms reported in the qualitative studies (i.e. itch, hair loss, pain, fatigue) were in accordance with previously mentioned quantitative studies. Pruritus was the most bothersome symptom, regardless of disease stage.[31] One of the most important ways in which itching affected patients daily lives was in their ability to sleep.[29–31] Overheating and discomfort were mentioned often and were reasons for no longer sharing a bed with their partner.[29]

Managing skin flaking was particularly effortful and time-consuming, with extensive routines regarding bathing, applying topical therapies and adjusting their clothing for comfort and minimizing embarrassment.[29–31]

MF and SS also resulted in limitations in practical daily life activities. Twelve out of 19 patients in the study of Demierre et al. (2011)[31] reported difficulty with travel by public transport or car due to painful or sensitive skin. Lack of energy prevented patients from accomplishing tasks at work and at home and secondary inability to concentrate due to fatigue or itching.[30] In the study of Demierre et al. (2011), 31% of patients desired to participate less in social activities since the diagnosis.[31]

Despite the symptom burden and its impact, participants described effective coping strategies. Central to these was drawing on emotional and practical support from family and friends.[29,32] Practical support included everyday assistance with application of topical agents, driving, accompanying to appointments, and help with household chores that patients were no longer able to do.[29] The disease also had a profound effect on caregivers.[32] Caregivers fulfilled multiple roles; acting as healthcare advocates, communicating with others about the patient's condition, attending appointments, providing medical and physical care (related to wounds and injections) and psychological support, housework and driving. A striking theme was the effect of CTCL on the relationship, communication and intimacy between caregiver and patient. Finally, patients also noted substantial treatment and financial burden.

Discussion

MF and SS have a significant effect on general- and skin specific quality of life. This review currently is the most extensive review of the literature providing an overview of the impact of the different stages of disease of MF and SS on the quality of life. In addition to previous literature,[7] the broader perspective and in-depth analysis of the significant impact of the different stages of disease on the different domains of dermatologic- and generic QoL provides a unique insight. The effect on QoL was found to be greater in patients with late-stage disease, with significant impairments on functional, emotional and physical domains. Significant influence of the disease on daily life activities were found.

This broad overview on QoL in MF/SS patients can be used in daily practice to help treating physicians gain awareness of this aspect of the patient's condition and provide tools for expectation management. Knowledge of QoL and illness perception is important because it identifies the patients perspective. This is critical in order to avoid misunderstanding and miscommunication in healthcare, since the treating physicians view on the same condition might differ.[23]

It remains important to incorporate QoL in to the assessments of treatment, for example, to identify patients with skin-directed therapies who experience an improved QoL and, therefore, clinical benefit despite failing to achieve a formal definition of treatment response.[24] Dalal et al.[8] found that targeted treatments, despite the demonstrating effects on distressing skin problems, also have a considerable symptom burden contributing to reduced patients QoL. As MF and SS have few curative options, treatments are predominantly palliative. Therefore, treatment should be aimed at minimizing symptoms and improving QoL.[20]

Current evidence suggests a considerable effect of CTCL on QoL, especially in late-stage MF/SS patients. This includes social and emotional domains. However, the guidelines for the management of CTCL do not include specific recommendations with regard to the supportive care needs of patients or their family/caregivers. Multidisciplinary assessment and management of both physical and psychological functioning is needed in order to improve the provided care for patients and their careers.[29] A referral to social workers, psychologists or sexologists in case of significant symptoms that heavily influence daily life activities or

relationships should be considered to reduce the burden of disease. While this has not been explored in CTCL patients, supportive care programmes have been proven effective in other cancer patients and may improve QoL.[53]

However, it must be stated that the impact of CTCL may be subject to large inter-individual differences. Also for pruritus, the threshold for distress caused by symptoms may vary from one patient to another.[23,54] Quantitative assessment tools are valuable to gain a snapshot of the impact of the disease, and allows comparison to other diseases and evaluation of treatment effects. However, the disease impacts multidimensional aspects of QoL beyond those captured in the standardized questionnaires, such as the consequences of skin flaking, inability of wearing clothing of their choice, affected sleep and other limitations regarding practical daily life activities.[29,30] Qualitative studies might more adequately reflect the specific clinical burden and consequences of the disease in daily life activities.[30] Therefore, a combination of qualitative methods and validated questionnaires is recommended to assess the influence of the different stages of MF/SS on the total aspects of QoL.[30]

Future studies would benefit from clearly distinguishing between diagnoses and disease stages when specifying the disease impact of CTCL on QoL, for example, studies should report separate results for MF and SS patients, and also differentiate between disease stages.[28] Not only the total scores, but also the different components of the instruments need to be reported separately in order to enhance comparison between the different domains of QoL and disease stages.

Limitations

Due to the heterogeneity in study populations, disease stages and used QoL instruments, pooling of data was not possible and the outcomes must be interpreted with caution. However by describing separate results for the different stages of disease, a practical overview of the current literature was provided that has not been described in the literature previously.

Furthermore, some results included in this review were based on variables not included as search terms in our systematic search. This was done in order to be able to report how different variables (e.g. pruritus) were correlated with QoL. As pruritis was the most frequent symptom reported by the QoL instruments, these data provide an additional insight. However, future studies should corroborate these results and minimize the possible influence of selection bias.

Conclusion

Mycosis Fungoides and Sézary Syndrome have a significant effect on dermatology-specific, cancer-specific and generic QoL. The effect on QoL was greater in patients with late-stage disease than early stage disease, with significant impairments on functional, emotional and physical domains. Pruritus was the most frequent reported and bothersome symptom. Results of this review underline the impact of different disease stages of CTCL on QoL and provide a structured overview of this impact that may be used to inform researchers and healthcare providers and create awareness on QoL impairments.

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Supporting information

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Supplementary Material.