Association of Cardiovascular Disease in Patients with Mycosis Fungoides and Sézary Syndrome Compared to a Matched Control Cohort

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Mycosis fungoides/Sézary syndrome (MF/SS) produces a low-grade chronic inflammatory state that may be associated with an increased risk of cardiovascular (CV) events, as seen in other chronic, systemic dermatologic diseases. To assess this association, a retrospective, cross-sectional study was designed in which 421 patients with a biopsy-proven diagnosis of MF/SS were compared with a control cohort of 4,210 age-, gender-, and race-matched patients randomly selected from the National Health and Nutritional Evaluation Survey database. The MF/SS cohort had a 14% prevalence of CV events, which was not statistically different from the control population's prevalence of 13%. In the MF/SS cohort, a multivariable logistic regression model showed that older patients (OR = 1.05 for each year of age, 95% confidence interval = 1.02−1.07) and those diagnosed with hypertension (OR = 3.40, 95% confidence interval = 1.71−6.75) had a higher risk of a CV event ($P < 0.001$). Risk factors such as gender, race, smoking, diabetes, and obesity were not significantly associated with CV events. Findings suggest that in the MF/SS population, advancing age and hypertension are risk factors for CV events, requiring clinical recognition and management. In addition, further research is needed to understand the complex interplay of how chronic inflammation in MF/SS impacts the immune development of CV disease.

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INTRODUCTION

Cutaneous T-cell lymphoma encompasses a group of lymphoproliferative neoplasms of skin-homing malignant T cells. This study focuses on the major subtypes of cutaneous T-cell lymphoma: mycosis fungoides (MF) and Sézary syndrome (SS). Although several chronic systemic dermatologic diseases (e.g., psoriasis and hidradenitis suppurativa [Duan et al., 2020; Reddy et al., 2020]) and hematologic malignancies (e.g., chronic myelomonocytic leukemia [Elbæk et al., 2019]) are associated with increased risk for cardiovascular (CV) events, there is insufficient data regarding the risk of CV events in MF or SS (Lindahl et al., 2016; Tsai et al., 2016)

Psoriasis and hidradenitis suppurativa are well-established examples of chronic cutaneous inflammatory diseases associated with CV disease (CVD). In psoriasis, activation of the T helper 1 immune pathway—through the activation of *IL-2*, *TNF-α*, and *INF-γ*—induces T-cell activity, antigen-presenting cells, and cytokines, facilitating the development of atherosclerosis and eventually CV events, including myocardial infarction. Furthermore, advanced age and disease severity in patients with psoriasis are associated with an increased risk of CVD (Aksentijevich et al., 2020; Gelfand et al., 2006). In hidradenitis suppurativa, increased proinflammatory markers such as *IL-6*, C-reactive protein, and *TNF-α* promote oxidative stress, endothelial dysfunction, and atherosclerosis (Reddy et al., 2020). Features of chronic inflammation, such as those seen in psoriasis and hidradenitis suppurativa, can also be found in MF. Mononuclear cells from tissue samples of patients with early-stage MF and psoriasis have high gene expression levels of *IL2*, *IL4*, and *IFN-γ*, which may contribute to the development of atherosclerosis and CVD (Chong et al., 2008; Krejsgaard et al., 2017).

Recent evidence suggests that long-term malignant proliferation and inflammation, such as in MF, may lead to increased coagulability and risk of venous thromboembolism (Eichinger, 2016; Falanga et al., 2015; Xu et al., 2010). In theory, treatments such as extracorporeal photopheresis and bexarotene, a retinoic acid, may increase the risk of CV events through increased coagulability and dyslipidemia, respectively. However, there are little data to substantiate such claims.

CVD continues to be the leading cause of mortality in 40% of patients aged >65 years. Given that the average age of MF/SS diagnosis is 55−60 years, it is critical to assess the association of CV events within this population (North and Sinclair, 2012). Clarifying CV event risk in MF/SS provides

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Abbreviations: CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; HTN, hypertension; MF, mycosis fungoides; NHANES, National Health and Nutritional Evaluation Survey; SS, Sézary syndrome

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crucial clinical direction regarding patient management and interdisciplinary care coordination. Whereas 25% of patients diagnosed with MF/SS will die from complications, most patients will succumb to other diseases, infections, or complications (Dummer et al., 2021). Therefore, understanding the role of comorbidities in this population is imperative.

A few studies from outside the United States have explored how CV comorbidities are associated with MF/SS, but their findings are inconsistent. For example, one study shows that patients with MF with advanced age and CV risk factors have an increased risk of stroke (Tsai et al., 2016). Another report indicates that the risk of myocardial infarction or stroke is elevated within the first 5 years after diagnosis of MF but not after that (Lindahl et al., 2016). To our knowledge, the association of CVD and related pre-existing comorbidities, including racial differences, has not been evaluated in patients with MF/SS within the US population.

In this study, we investigate the association of CV events in the MF/SS patient population of a US-based single tertiary referral center compared with that in a matched population from the National Health and Nutritional Evaluation Survey (NHANES). Our secondary objective is to determine the effect of gender, race, age, smoking, diabetes mellitus, hypertension (HTN), and obesity on the risk of CV events in the MF/SS population.

RESULTS

MF/SS and control cohort demographics

There were 421 patients with MF/SS in this study. To compare the association of CV events in the MF/SS population with that in a US population, a matched control population of 4,210 patients was generated from 20 years of unique patient data from the NHANES dataset. Descriptive data of these two populations are presented in Table 1. After demographically matching for age, gender, and race, each cohort had a slight majority of White ethnicity (MF/SS n = 225/421; control n = 2,240/4,210; 53%) and an average age of 59 years. However, patients from all other races (including Black, Latinx, Asian, Middle Eastern, other, and not specified) were significantly younger (mean age = 59 years for White patients vs. 49 years for patients from all other races, $P < 0.001$) than the White population. Most patients (51%) were female (MF/SS n = 214/421; control n = 2,158/4,210; $P = 0.91$). The MF/SS population had statistically fewer smokers than the control population (n = 153/421 [36%] vs. n = 2,186/4,210 [52%]; $P < 0.001$). There were statistically more patients with MF/SS diagnosed with diabetes mellitus (n = 70/421 [17%] vs. n = 475/4,210 [11%]; $P = 0.002$) and HTN than the control group (n = 204/421 [48%] vs. n = 1,628/4,210 [39%]; $P < 0.001$). There was no significant difference in the number of patients diagnosed with obesity (n = 135/421 [32%] vs. n =

Table 1. Characteristics of MF/SS Cohort Versus Demographic-Matched Control Cohort

Characteristics	MF/SS	Control	
All	**n = 421**	**n = 4,210**	***P*-Value**
Gender (%)			
Male	207 (49)	2,052 (49)	0.91
Female	214 (51)	2,158 (51)	
Age by race subgroup, y (average ± SD)			
White	59 (15.4)	59 (15.1)	0.80
All other races[1]	49 (15.8)	49 (15.5)	0.87
Ethnicity (%)			
White	225 (53)	2,240 (53)	0.97
All other races[1]	196 (47)	1,970 (47)	
Smoke history (%)			
Never	268 (64)	2,024 (48)	<0.001
Ever/current	153 (36)	2,186 (52)	
Diabetes (%)			
No	351 (83)	3,735 (89)	0.002
Yes	70 (17)	475 (11)	
Hypertension (%)			
No	217 (52)	2,582 (61)	<0.001
Yes	204 (48)	1,628 (39)	
Obesity (%)			
No	286 (68)	2,662 (63)	0.063
Yes	135 (32)	1,548 (37)	
CV event (%)			
No	360 (86)	3,672 (87)	0.36
Yes	61 (14)	538 (13)	

Abbreviations: CV, cardiovascular; MF, mycosis fungoides; SS, Sézary syndrome.

Shown are characteristics of the MF/SS cohort compared with those of the age-, gender-, and race-matched control cohort. The control cohort was matched to MF/SS cohort at a 1:10 ratio using propensity score. Entries in the first two columns are count (%), where percentages are of the total for each cohort. The age average is reported in years. Group differences for continuous variables were based on a two-sample *t*-test and listed in the average row. Group differences for categorical variables were based on chi-square. Percentage is denoted as the percentage before/during the monitoring screening period for a chunk of variables (column marginal).

[1]All other races including Black, Latinx, Asian, Middle Eastern, other, and not specified.

1,548/4,210 [37%]; $P = 0.063$). The prevalence of CV events was not significantly different between the two groups (n = 61/421 [14%] vs. n = 538/4,210 [13%]; $P = 0.36$). In addition, a multivariable model adjusting for smoking status, diagnosis of diabetes, HTN, and obesity did not reveal a difference in the risk of CV events between the MF/SS group and the matched control group (OR = 1.03, 95% confidence interval [CI] = 0.76–1.40).

Subgroup analyses were conducted to test the interaction effect on the risk of CV events between the MF/SS cohort (vs. controls) and demographic variables, and no significant differences between MF/SS and demographic-matched controls in the specified subgroups were identified.

CV events within the MF/SS population

We assessed CV events and risk factors within the MF/SS population and described our results in Table 2. A list of the subtypes of CV events is outlined in Supplementary Table S1. Advanced age was a significant risk factor for CV events, and the odds of CV events in the MF/SS population increased by 5% (95% CI = 3–8%) for each year of age. The odds of a female patient having a CV event were almost less than half of that of a male patient (OR = 0.54, 95% CI = 0.30–0.93; $P = 0.028$). There was no significant difference in the occurrence of CV events between White and patients from all other races (OR = 0.60, 95% CI = 0.34–1.05) or between patients with early-stage and those with late-stage MF/SS (OR = 1.59, 95% CI = 0.76–3.13).

Concerning CV risk factors, smoking (OR = 1.86, 95% CI = 1.08–3.23, $P = 0.026$) and the diagnosis of HTN (OR = 4.83, 95% CI = 2.60–9.58, $P < 0.001$) were significantly associated with higher odds of a CV event. Other CV risk factors, such as a diagnosis of diabetes or obesity, did not have a statistically significant association with the presence of CV events in the MF/SS population. There was no statistically significant difference in the prevalence of CV events between patients with MF/SS who had ever received a retinoid or extracorporeal photopheresis treatment and those who had never received these treatments (14% vs. 15%, OR = 0.93 [95% CI = 0.46–1.76]).

Regression models of CV events in MF/SS population and matched control population

Presented in Table 3 are the findings from the multivariable logistic regression models developed to independently predict a CV event within the MF/SS cohort and the control cohort. Within the MF/SS cohort, older patients (OR = 1.05 for each year of age, 95% CI = 1.02–1.07; $P < 0.001$) and those diagnosed with HTN (OR = 3.40, 95% CI = 1.71–6.75; $P < 0.001$) had a higher chance of developing a

Table 2. Univariable Logistic Regression Model of CV Events in the MF/SS Cohort

	Total MF/SS Cohort	No CV Event	CV Event		
Variables	**n = 421**	**n = 360**	**n = 61**	**OR (95% CI)**	***P*-Value**
Age (average ± SD), y	54 ± 16.4	52 ± 16.1	65 ± 14.1	1.05 (1.03–1.08)	<0.001
Gender (%)					
Male	207 (49)	169 (82)	38 (18)	1	0.028
Female	214 (51)	191 (89)	23 (11)	0.54 (0.30–0.93)	
Race (%)					
White	225 (53)	186 (83)	39 (17)	1	0.078
All other races[1]	196 (47)	174 (89)	22 (11)	0.60 (0.34–1.05)	
Stage of disease					
Early (IA–IIA)	361 (86)	312 (86)	49 (14)	1	0.19
Late (IIB–IVB) Sézary	60 (14)	48 (80)	12 (20)	1.59 (0.76–3.13)	
Smoke history (%)					
Never	268 (64)	237 (88)	31 (12)	1	0.026
Ever/current	153 (36)	123 (80)	30 (20)	1.86 (1.08–3.23)	
Diabetes (%)					
No	351 (83)	304 (87)	47 (13)	1	0.15
Yes	70 (17)	56 (80)	14 (20)	1.62 (0.81–3.07)	
Hypertension (%)					
No	217 (52)	204 (94)	13 (6)	1	<0.001
Yes	204 (48)	156 (76)	48 (24)	4.83 (2.60–9.58)	
Obesity (%)					
No	286 (68)	247 (86)	39 (14)	1	0.47
Yes	135 (32)	113 (84)	22 (16)	1.23 (0.69–2.16)	
Tx w/Ret/ECP (%)					
No	327 (78)	279 (85)	48 (15)	1	0.84
Yes	94 (22)	81 (86)	13 (14)	0.93 (0.46–1.76)	

Abbreviations: CI, confidence interval; CV, cardiovascular; ECP, extracorporeal photopheresis; MF, mycosis fungoides; Ret, retinoid; SS, Sézary syndrome.
Univariable analysis to predict CV event within the MF/SS cohort is presented. Entries in the first three columns are count (%); percentages under the first column are of the total cohort, and percentages under each event are of each separate factor. OR is based on logistic regression with corresponding *P*-values for testing the OR = 1. Tx w/Ret/ECP indicates that Ret and/or ECP were administered before a CV event occurred.
[1]All other races including Black, Latinx, Asian, Middle Eastern, other, and not specified.

Table 3. Multivariable Logistic Regression Model of CV Event by Cohort

Variables	MF/SS Cohort OR (95% CI)	*P*-Value	Control Cohort OR (95% CI)	*P*-Value
Age (per 1 y)	1.05 (1.02–1.07)	<0.001	1.06 (1.05–1.06)	<0.001
Gender (%)				
Male	1		1	
Female	0.61 (0.33–1.13)	0.116	0.68 (0.55–0.85)	<0.001
Race (%)				
White	1		1	
All other races[1]	0.86 (0.45–1.66)	0.652	0.87 (0.70–1.08)	0.20
Smoke history (%)				
Never	1		1	
Ever/current	1.28 (0.71–2.33)	0.414	1.67 (1.35–2.06)	<0.001
Diabetes (%)				
No	1		1	
Yes	1.18 (0.57–2.43)	0.654	2.09 (1.63–2.68)	<0.001
Hypertension (%)				
No	1		1	
Yes	3.40 (1.71–6.75)	<0.001	2.75 (2.23–3.40)	<0.001
Obesity (%)				
No	1		1	
Yes	1.53 (0.81–2.89)	0.193	1.17 (0.95–1.44)	0.15

Abbreviations: CI, confidence interval; CV, cardiovascular; MF, mycosis fungoides; SS, Sézary syndrome.

A multivariable logistic regression model was used to determine the risk factors of developing CV events for each independent cohort. The control cohort was matched to the MF/SS cohort by age, gender, and race.

[1]All other races including Black, Latinx, Asian, Middle Eastern, other, and not specified.

CV event. No statistically significant associations were found between gender, race, smoking, diabetes, or obesity and the presence of CV events, although a smaller sample size lowered the statistical power.

In the control population, older age was a significant predictor of CV events (OR = 1.06 for each year of age, 95% CI = 1.05–1.06; $P < 0.001$), and female gender was associated with a lower risk of CV events (OR = 0.68, 95% CI = 0.55–0.85; $P < 0.001$). Of the risk factors assessed, smoking (OR = 1.67, 95% CI = 1.35–2.06), a diagnosis of diabetes (OR = 2.09, 95% CI = 1.63–2.68), and a diagnosis of HTN (OR = 2.75, 95% CI = 2.23–3.40) were associated with a significantly higher risk of a CV event in the control population ($P < 0.001$). Race and obesity were not significantly predictive of CV events in the control population.

DISCUSSION

This United States–based retrospective study builds on the minimal data available regarding the association between MF/SS and CVD, providing requisite information for the holistic care of patients with incurable chronic malignancies. Consistent with the known MF/SS prevalence, almost half of the population in this MF/SS cohort was from races that did not identify as White (including Black, Latinx, Asian, Middle Eastern, other, and not specified), providing more demographically representative study than previously published data in the literature (Bradford et al., 2009; Korgavkar et al., 2013).

Given the chronic inflammatory state of MF/SS, the lack of difference in the prevalence of CV events between the patient and control cohorts is notable. A rationale for this finding may lie in the disease biology and its complex interaction of immune cells, including $CD8^+$, $CD4^+$, regulatory T cells, and malignant T cells. In MF, malignant T cells present with varying levels of effector molecules and coinhibitory receptors, which affect the antitumor immune response and may inadvertently impact atherosclerosis development (Gaydosik et al., 2019). In atherosclerosis, regulatory T cells secrete *IL-10*, which prevents plaque formation and promotes a stable plaque phenotype in established disease (Meng et al., 2016). In MF/SS, malignant T cells adopt a regulatory T cell–like phenotype through increased expression of *CD25/CTLA-4/FOXP3* and function by secreting *IL-10* and *TGF-β* (Berger et al., 2005; Meng et al., 2016). Higher levels of *IL-10* are found in MF tissue than in healthy controls; thus, MF/SS may mitigate the effects of certain CV risk factors by blunting the proinflammatory response necessary for atherosclerosis development (Asadullah et al., 1996).

In MF, chronically stimulated $CD8^+$ T cells overexpress inhibitory checkpoint receptors (i.e., PD-1 and CTLA-4), leading to an exhausted phenotype that cannot respond appropriately to pathogens and tumor antigens. This T-cell exhaustion in turn compromises immune surveillance, enables tumor growth, and further suppresses T helper 1 antitumor immunity (Durgin et al., 2021; Querfeld et al., 2018). These exhausted $CD8^+$ T cells from patients with SS have demonstrated a decreased complexity of the TCR repertoire, further impairing T-cell growth and function (Dummer et al., 2021). T-cell exhaustion and receptor dysregulation may dampen the effects of conventional T-cell mechanisms that promote atherosclerosis and account for the variance in risk factors that predict CV events in the MF/SS population.

HTN and advanced age were expected predictors of CV events in the MF/SS and the matched control populations. Because HTN is a modifiable risk factor, it is prudent for providers to ensure close HTN management in the MF/SS

population, ideally coordinating with the patient's primary care providers. Moreover, the theoretical potential of MF/SS treatments, such as extracorporeal photopheresis or retinoids, to contribute to CV events in the MF/SS population was considered. Findings from this study did not indicate an association between these treatments and CV events, which is consistent with current evidence (Lindahl et al., 2018).

The nonpredictive value of race on CV event development in both cohorts contradicts general observations. Black/African American patients experience a higher burden of CVD, irrespective of socioeconomic status, and this is a considerable contributor to the racial disparity in life expectancy in the United States (Bell et al., 2018; Carnethon et al., 2017). The significantly younger age of our patients from all other races (including Black, Latinx, Asian, Middle Eastern, other, and not specified) and consequently their matched control group may explain the lack of increased CV event prevalence in this group. Furthermore, we performed our analysis on populations defined as White versus all other races. The population from all other races includes a small number of patients that were not Black/African American (7.8%), which could conceal differences.

Although the univariable analysis suggested that female patients with MF/SS had a lower risk of CV events than their male counterparts, this finding was not supported in the multivariable analysis and remained to be determined. Notably, this finding held in the multivariable analysis of the control cohort.

Interestingly, our study did not show a statistically significant association between obesity and CV events in either the control or the MF/SS group. This finding was further validated by a lack of predictive value in the multivariable regression model. Although obesity is conventionally thought to be associated with an increased risk of CV events, there is growing evidence of an obesity paradox more prevalent in the elderly population, which suggests that patients with overweight or mild obesity have a better short- and medium-term prognosis of CVD than leaner patients (Lavie et al., 2018; McAuley and Beavers, 2014). This finding may be clarified with a longer follow-up and illustrates one of the limitations inherent to the retrospective nature of our study.

This study demonstrates that patients with MF/SS do not have a higher association of CV events than an age-, gender-, and race-matched control population. Although advanced age and HTN do increase the risk of CV events in patients with MF/SS, other known risk factors such as race, gender, smoking, and diabetes have an unclear role in the expression of CV events. This study uses a publicly available dataset to construct a representative matched cohort. The results elicit interest in the underlying MF/SS biological mechanisms modulating CV risk factors and potential events. Further research is necessary, including a multicenter prospective cohort study to validate these results and molecular-level investigation to elucidate the interplay between MF/SS and the immune milieu impacting CVD.

MATERIALS AND METHODS

Study design

In this cross-sectional study, a retrospective analysis of the Johns Hopkins Health System electronic medical database from January 2011 to June 2019 for all patients aged >18 years diagnosed with MF/SS was conducted. Information was collected on patient demographics, clinical characteristics, disease stage, and treatments. All included patients had biopsy-proven MF or SS as determined by a dermatopathologist. We classified MF/SS diagnoses on the basis of the World Health Organization-European Organization for Research and Treatment of Cancer classification of cutaneous lymphomas and determined overall staging using the TNMB (tumor-node-metastasis-blood) system (Olsen et al., 2007; Willemze et al., 2005). In this study, early-stage disease is defined as stages IA–IIA, and late-stage disease is defined as IB–IVB or SS.

The NHANES is a nationally representative annual survey collected by the Centers for Disease Control and Prevention to assess the general health and nutritional status of the US population (Centers for Disease Control and Prevention, 2018). To compare the association of CV events in the MF/SS population, a control population of patients was derived from the NHANES database from 1999 to 2018 utilizing a propensity score demographic matching approach. Because MF/SS is a rare disease with a prevalence of 0.77–0.87 per 100,000 population in the United States, it is assumed that participants in the NHANES study did not have MF/SS (Dobos et al., 2020).

Covariates and outcomes

Cardiac risk factors, as defined by the American Heart Association guidelines, included any diagnosis of essential HTN, history of former or current smoking, history of type 2 diabetes mellitus, or history of obesity as measured by body mass index. In addition, we obtained race and gender information from the demographic section of the electronic medical record. A CV event was defined as any diagnosis of the following: myocardial infarction, stroke/cerebrovascular accident, peripheral arterial occlusive disease, abdominal aortic aneurysm, peripheral vascular disease, and other types of CVD that do not fit into these categories. We counted CV events at any time, regardless of when patients received a disease diagnosis of MF/SS.

Statistical analysis

Demographic matching was performed at a 1:10 (MF/SS: NHANES) ratio without replacement on the basis of propensity score, with caliper width set at 0.2 of the SD of the propensity score to identify a cohort of patients with demographic characteristics similar to those of patients with MF/SS (Austin, 2011). Demographic characteristics for matching included age of diagnosis for MF/SS cases compared with age at participation date for NHANES controls (continuous), gender (male vs. female), and race (White vs. all other races, including Black, Latinx, Asian, Middle Eastern, other, and not specified). After selecting the demographic-matched controls, the risk factors of CV events in the NHANES and MF/SS databases were extracted, including smoking status (never vs. ever/current) and the presence or absence of the following: diabetes, HTN, and obesity. Descriptive measurements for baseline characteristics were compared between MF/SS population and the matched control population using χ^2 test for categorical variables and two-sample *t*-test for continuous variables. The odds of CV events in MF/SS were compared with those in demographic-matched controls by adjusting the risk factors of CV events using logistic regression, where the inclusion criteria of the adjustment were based on the testing results for group difference with $P < 0.10$.

All analyses were compiled in R, version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria). *P*-values of <0.05 were the

cut point for statistical significance without adjusting multiplicity in an exploratory manner. *P*-values of <0.10 were presented using three digits to the right of the decimal except in cases where the third digit was zero. Model results are reported as OR with 95% CI.

Protections of study subjects

All identifiers were removed before data analysis. The study was approved by the Johns Hopkins Institutional Board of Review.

Data availability statement

Datasets related to this article can be found at https://doi.org/10.17632/xwc7rjdvh6.1, an open-source online data repository hosted at Mendeley Data (Johnson et al., 2022; unpublished data).

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CONFLICT OF INTEREST

The authors state no conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization: CMJ, SR; Data Curation: CMJ, BB, MC, PK, SR; Formal Analysis: HT, RV; Investigation: CMJ, SR; Methodology: CMJ, SR; Validation: CMJ, SMT, HT, RV, SR; Writing - Original Draft Preparation: CMJ, SR; Writing - Review and Editing: CMJ, SMT, SR

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.xjidi.2023.100219.

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Supplementary Table S1. Cardiovascular Events in MF/SS Cohort

Cardiovascular Event	Events
MI	19
Stroke/CVA	7
Cardiovascular disease, other[1]	17
Peripheral arterial disease	4
Aortic abdominal aneurysm	6
Peripheral vascular disease	8

Abbreviations: CVA, cerebrovascular accident; MF, mycosis fungoides; MI, myocardial infarction; SS, Sézary syndrome.

The breakdown of each type of cardiovascular event in the MF/SS cohort is shown.

[1]Cardiovascular disease, other includes types of heart disease that do not fit into the categories mentioned.