

JULIA SCARISBRICK (Orcid ID : 0000-0002-8011-4408)

PROFESSOR RUDOLF STADLER (Orcid ID : 0000-0003-2683-6028)

DR VASILIKI A NIKOLAOU (Orcid ID : 0000-0001-9340-9152)

Article type : Original Article

## The PROCLIFI international registry of early stage Mycosis Fungoides identifies substantial diagnostic delay in most patients

### Running Header / Short Title:

PROCLIFI Study investigating Prognostic Factors in Early Stage MF

J.J. Scarisbrick<sup>1-4</sup>, P. Quaglino<sup>2,3</sup>, H.M. Prince<sup>3</sup>, E. Papadavid<sup>2,3</sup>, E. Hodak<sup>2,3</sup>, M. Bagot<sup>2,3</sup>, O. Servitje<sup>2,3</sup>, E. Berti<sup>2,3</sup>, P. Ortiz-Romero<sup>2,3</sup>, R. Stadler<sup>2,3</sup>, A. Patsatsi<sup>2,3</sup>, R. Knobler<sup>2,3</sup>, E. Guenova<sup>2,3</sup>, V. Nikolaou<sup>2,3</sup>, C. Tomasini<sup>2</sup>, I. Amitay<sup>2,3</sup>, H. Prag Naveh<sup>2,3</sup>, C. Ram-Wolff<sup>2</sup>, M. Battistella<sup>2,3</sup>, S. Alberti-Violetti<sup>2</sup>, R. Stranzenbach<sup>2,3</sup>, V. Gargallo<sup>2</sup>, C. Muniesa<sup>2</sup>, T. Koletsa<sup>2</sup>, C. Jonak<sup>2,3</sup>, S. Porkert<sup>2</sup>, C. Mitteldorf<sup>2</sup>, T. Estrach<sup>2</sup>, A. Combalia<sup>2</sup>, M. Marschalko<sup>2</sup>, J. Csomor<sup>2</sup>, A. Szepesi<sup>2</sup>, A. Cozzio<sup>2,3</sup>, R. Dummer<sup>2</sup>, N. Pimpinelli<sup>2</sup>, V. Grandi<sup>2</sup>, M. Beylot-Barry<sup>2</sup>, A. Pham-Ledard<sup>2</sup>, M. Wobser<sup>2</sup>, E. Geissinger<sup>2</sup>, U. Wehkamp<sup>2,3</sup>, M. Weichenthal<sup>2</sup>, R. Cowan<sup>2,4</sup>, E. Parry<sup>2,4</sup>, J. Harris<sup>4</sup>, R. Wachsmuth<sup>2,4</sup>, D. Turner<sup>4</sup>, A. Bates<sup>4</sup>, E. Healy<sup>4</sup>, F. Trautinger<sup>2,3</sup>, J. Latzka<sup>2</sup>, J. Yoo<sup>1,2</sup>, B. Vydianath<sup>1</sup>, R. Amel-Kashipaz<sup>1</sup>, L. Marinou<sup>2</sup>, A. Oikonomidi<sup>2</sup>, A. Stratigos<sup>2</sup>, M.-D. Vignon-Pennamen<sup>2</sup>, M. Battistella<sup>2</sup>, F. Climent<sup>2</sup>, E. Gonzalez-Barca<sup>2</sup>, E. Georgiou<sup>2</sup>, R. Senetta<sup>2</sup>, P. Zinzani<sup>2</sup>, L. Vakeva<sup>2</sup>, A. Ranki<sup>2</sup>, A.-M. Busschots<sup>2</sup>, E. Hauben<sup>2</sup>, A. Bervoets<sup>2</sup>, F.J. Sherida Woei-A-Jin<sup>2</sup>, R. Matin<sup>4</sup>, G. Collins<sup>4</sup>, S. Weatherhead<sup>4</sup>, J. Frew<sup>4</sup>, M. Bayne<sup>4</sup>, G. Dunnill<sup>4</sup>, P. McKay<sup>4</sup>, A. Arumainathan<sup>4</sup>, R. Azurdia<sup>4</sup>, K. Benstead<sup>4</sup>, R. Twigger<sup>3</sup>, K. Rieger<sup>3</sup>, R. Brown<sup>3</sup>, J.A. Sanchez<sup>3</sup>, D. Miyashiro<sup>3</sup>, O. Akilov<sup>3</sup>, S. McCann<sup>3</sup>, H. Sahi<sup>3</sup>, F.M. Damasco<sup>3</sup>,

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/bjd.17258](https://doi.org/10.1111/bjd.17258)

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C. Querfeld<sup>3</sup>, A. Folkes<sup>3</sup>, C. Bur<sup>3</sup>, C.-D. Klemke<sup>2</sup>, P. Enz<sup>3</sup>, R. Pujol<sup>2,3</sup>, K. Quint<sup>2</sup>, L. Geskin<sup>3</sup>, E. Hong<sup>3</sup>, F. Evison<sup>1</sup>, M. Vermeer<sup>2,3</sup>, L. Cerroni<sup>2</sup>, W. Kempf<sup>2</sup>, Y. Kim<sup>3</sup>, R. Willemze<sup>2</sup>

<sup>1</sup> European Co-ordinating PROCLIP Centre for PROCLIP, University Hospitals Birmingham, Birmingham, UK

<sup>2</sup> Member of the European Organisation of Research and Treatment of Cancer (EORTC), Cutaneous Lymphoma Task Force

<sup>3</sup> Member of the Cutaneous Lymphoma International Consortium (CLIC)

<sup>4</sup> Member of the UK Cutaneous Lymphoma Group

Acknowledgement of Research Support -Funding Information:

Cancer Research UK (50763/A18021) Dr. Julia Jane Scarisbrick

European Academy Dermatology Venerology (2014-23) Dr. Julia Jane Scarisbrick

Spatz Foundation; Sundown Endowment Legacy, Dr. Youn-Hee Kim

Krebsliga Schweiz (KFS-4243-08-2017) Dr Emmanuella Guenova

Promedica Stiftung 1406/M and 1412/M Dr Emmanuella Guenova

**Corresponding Author: Dr Julia Scarisbrick,**

**Email: [julia.scarisbrick@uhb.nhs.uk](mailto:julia.scarisbrick@uhb.nhs.uk)**

**Not previously presented or published works**

**No disclaimers or conflicts of interest**

**What's already known about this topic?**

- MF is a rare skin cancer which may closely mimic common inflammatory dermatoses in early stage disease
- There is no singular diagnostic test for mycosis fungoides
- Diagnosis of early stage mycosis fungoides requires close clinical, pathologic and genotypic correlation

**What does this study add?**

- This study reports on the clinical characteristics of a large international cohort of early-stage MF patients whose diagnosis has been confirmed centrally following clinicopathologic review

- The median age of presentation is 57yrs which is significantly younger than those presenting with advanced-stage MF at 66yrs
- This study confirmed a worldwide male predominance in early-stage MF (1.7males:1female)
- A diagnostic delay of early-stage MF is frequent with a median delay of 3 years

## Abstract

Survival in mycosis fungoides (MF) is varied and may be poor. PROCLIP (PROspective Cutaneous Lymphoma International Prognostic Index) Study is a web-based data collection system for early-stage MF with legal data sharing agreements permitting international collaboration in a rare cancer with complex pathology. Clinicopathological data must be 100% complete and in-built intelligence in the database system ensures accurate staging.

Pre-defined datasets for clinical, haematological, radiological, immunohistochemical, genotypic, treatment and quality-of-life are collected at first diagnosis of MF and annually to test against survival with the aim of developing a prognostic index. Biobanked tissue samples are recorded within a Federated Biobank for translational studies.

430 patients were enrolled from 29 Centres in 15 countries spanning 5 continents. 348 were confirmed as early-stage MF at Central Review. The majority had classical MF (81.6%) with a CD4 phenotype (88.2%). Folliculotropic MF was diagnosed in 17.8%. Most presented with stage I (IA:49.4%,IB:42.8%) but 7.8% presented with enlarged lymph nodes (stage IIA). A diagnostic delay between first symptom development and initial diagnosis was frequent (85.6%), with a median delay of 36 months (interquartile range=12-90 months). This highlights the difficulties in accurate diagnosis, which is contributed by lack of a singular diagnostic test for MF.

This confirmed early-stage MF cohort is being followed-up to identify prognostic factors, which may allow better management and improve survival by identifying patients at risk of disease progression. This study design is a useful model for collaboration in other rare diseases, especially where pathological diagnosis can be complex.

**CPMS ID 17662 (PROCLIP), RRK4970**

## Introduction

Mycosis fungoides (MF) is a rare cancer with an incidence of <1 per 100,000 but much higher prevalence given the long survival in early-stage disease (stages IA-IIA)<sup>1</sup>.

Meaningful studies in rare disease require large-scale international collaboration to power them. Such collaboration requires expert co-ordination, accessible data collection systems and legal data share agreements to be implemented which is challenging. Here we present the PROCLIP (PROspective International Cutaneous Lymphoma Prognostic Index) Study for early-stage MF as a prototype study for international collaborations in rare disease and present our initial findings and central review process.

Diagnosis of early-stage MF (IA-IIA) is complex due to a number of factors including varied clinical appearance and similarity to inflammatory skin diseases such as eczema/psoriasis, subtle variations in pathological/immunohistochemical features and lack of a singular specific diagnostic test. Indeed, inter-observer variation for diagnosis of T-cell lymphomas, including MF is well recognized and a definite diagnosis often requires careful clinicopathologic correlation with discordance in diagnosis ~20%<sup>2</sup>. Hence misdiagnosis and diagnostic delay are frequent. To confirm diagnosis in PROCLIP, all recruited patients were subject to expert central clinicopathological review. This is of paramount importance to ensure patients meet criteria for a diagnosis of early-stage MF and those with benign inflammatory dermatoses are rejected.

Patients with early-stage MF typically have a slowly progressive evolution over years or even decades to widespread patches or more infiltrated plaques. Morbidity can be considerable with pain, pruritus and disfigurement and patients have been demonstrated to have a poor quality of life<sup>3,4</sup>. However, disease specific mortality may occur in some patients<sup>5</sup> and up to one-third of patients presenting with early-stage disease progress within 10 years to advanced stage [IIB-IVB]<sup>6</sup> characterized by cutaneous tumours or erythroderma and/or nodal/leukaemic/visceral involvement. If patients with a poor prognosis could be pre-selected and referred for more intensive management there may be improved disease control and potentially survival. Given the rarity of MF, only a large international multicentre prospective study will improve our understanding and allow better diagnostic tests for more efficient diagnosis.

Specific clinical characteristics have been associated with a worse prognosis in MF. However, most are associated with advanced-stage disease and their relevance in early-stage disease is unknown. These include male sex, higher age, raised serum lactate dehydrogenase (LDH) and histological features such as folliculotropism<sup>7-12</sup> and large cell transformation (LCT)<sup>11-17</sup>. Some favourable prognostic factors have been identified for early-stage disease and include poikiloderma<sup>18</sup>, hypopigmented patches, a CD8+ve phenotype<sup>19</sup> and co-existing lymphomatoid papulosis<sup>16,20,21</sup>. However, these studies are typically single-centre cohorts and there is frequent discordance between reports. Benton et al 2013 developed a CLIP but future publications could not validate this<sup>5,22</sup> and large  
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international collaborations are required to develop useful PI's. An international PI may select patients with early MF at higher risk of disease progression for improved management choices.

## **METHODS:**

### **Study Design & Patients**

Datasets [Appendix I] were prospectively defined by the Cutaneous Lymphoma International Consortium (CLIC) over a series of meetings and teleconferences (2012-2014). A secure web-based data system was designed by University Hospital Birmingham (UHB) with in-built intelligence to stage patients which does not allow data to be saved unless clinicopathological datasets are complete<sup>1</sup>. Selected fields are duplicated to cross-check for data consistency. No patient identifiable data are shared and patients are anonymised centrally.

Specialist international centres treating MF were selected via Membership to expert international groups (European Organization for Research and Treatment of Cancer (EORTC), International Society for Cutaneous Lymphoma (ISCL)). A data sharing agreement was signed between each participating Centre and UHB<sup>2</sup>.

Since July 2015, all patients referred to the participating centres with a new diagnosis of early-stage MF within the prior 6 months were eligible. The study was reviewed and approved by local ethical committees/institutional review boards prior to recruitment. Patients were given verbal and written patient information about PROCLIFI in their native language. Written consent for participation in this study, analysis of data and use of blood, skin and lymph tissue for future translational research (Federated Biobank) was obtained at trial entry.

For each recruited patient data on clinical, haematological, pathological, lymph nodes, viscera, bone marrow, genotypical, treatment and quality-of-life information<sup>3</sup> (Skindex–29, Appendix I) is collected at time of diagnosis and updated annually or earlier in the event of disease stage progression or death [Appendix II]. The time in months from onset of MF lesions (as reported by the patient) and first diagnosis of MF at their Centre was recorded to investigate any delay in diagnosis. Delay in diagnosis includes both failure of patients to present to physicians and physicians delay and was pre-defined as the time from

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<sup>1</sup> This database is housed on a secure UHB server which is a secure SQL Server housed behind Threat Management Gateway (TMG's) and firewalls. The security of both the web application and technical infrastructure has been penetration tested by an independent ethical hack/security company.<sup>1</sup>

<sup>2</sup> On most occasions the generic agreement was signed but due to the complexity of data sharing and different stipulations between countries, if required, minor amendments were made.

<sup>3</sup> Quality of life data to be recorded using USA Skindex 29 questionnaire (permission granted by MAPI Research Trust, Lyon, France) with translations into English, Spanish, German, Dutch & Italian

occurrence of the patient's first skin lesions and a clinicopathological diagnosis made by their clinician. Note, this time didn't include the time to central pathology review.

### **Data Monitoring**

The PROCLIP database has an in-built intelligence system which creates email alerts for missing or overdue data, disallows saving of numerically impossible/highly unlikely data, prevents saving of incomplete data and autocalculates mSWAT (modified severity weighted assessment tool) which reflects skin tumour burden and provides a numerical value between 0-400<sup>23-24</sup>, blood classification and overall stage (using TNMB)<sup>25</sup>.

Additionally, a Data Monitoring Committee, DMC, [Appendix III] manually reviews data for inaccuracies. Queries are raised to the respective institutions if data inaccuracies are suspected and for missed updates.

### **Central Review**

All patients were subject to a clinicopathological review prior to the patient's data being included in the analysis. This was performed to confirm early-stage MF and prevent inclusion of patients with either reactive skin changes or advanced MF. Three internationally recognised leading dermatologists and dermatopathology specialists formed the Central Review panel (RW,LC,WK). The diagnosis of early-stage MF was based on a combination of clinical, histopathologic and immunophenotypic criteria, as published previously<sup>2</sup>. An initial Virtual-Review of representative clinical photographs of cutaneous lesions together with photomicrographs of Haematoxylin & Eosin, CD3, CD4 and CD8 stains was performed. In unclear cases slides were requested for a Real-Time Central Review. Details of the review processes are described in Appendix IV.

### **Statistical Analysis**

The Kruskal-Wallis test was used to analyse difference in medians for the non-parametric continuous variables. The Chi-squared test was used to determine differences in categorical variables. Variables are presented as medians and interquartile ranges for the non-parametric continuous variables. Analyses were performed using STATA SE v15 (StataCorp LP, College Station, Tex, USA).

## **RESULTS**

### **Central Review**

29 international Centres enrolled 430 patients [Fig.1]. Centres unable to comply with the Central Review process were not eligible for this study. Virtual Central Review confirmed 329 patients as early-stage MF. 64 were referred for a Real-Time Central Review and 37

failed (13 advanced-stage and 24 non-diagnostic of MF). Real-time review has been possible for 41/64 patients with 19/41 (46.3%) passing. At the time of manuscript writing, 23 are awaiting real-time review thus, 407/430 patients have completed central review; 348/407 patients were confirmed as early-stage MF (85.5%), 16/407 considered advanced-stage disease (3.9%) and 43/407 not diagnostic of MF (10.6%) [Flow diagram of central review results shown in Figure 2].

This report focuses on the 348 patients passing the central review process. However, all patients entered into the PROCLIFI database are followed-up as it is appreciated some of these patients may develop MF or have true MF which could not be confirmed by the Central Review process. In-reality all these patients may be receiving MF treatment from their local Centre.

### **Patient Demographics**

Of the 348 patients there was a male predominance with 219 males and 129 females (ratio 1.7:1). Table 1 shows the clinical characteristics.

The clinical stage was IA in 172 (49.4%), IB in 149 (42.8%) and IIA in only 27 patients (7.8%). The median age at diagnosis was 57 years (interquartile range (IQR)=44-67yrs), without significant differences between stage IA (median age=54yrs, IQR=44-66yrs), stage IB (median age=57, IQR=45-67yrs) and stage IIA (median age=61yrs, IQR=44-73yrs)  $P=0.285$ . 298 patients (85.6%) reported a diagnostic delay with a median delay of 36 months (IQR=12,90). This was similar in all stages ( $p=0.1410$ ); 36 months (IQR=12-72months) for stage IA, 48months (IQR=24-100months) for IB and 33 months (IQR=15-87) for IIA. ECOG scores were 0 in 338 patients, 1 in 8 patients, 2 in 1 patient and 4 in 1 patient.

The median mSWAT score at diagnosis of stage IA was 5 (IQR=2-8), IB was 26 (IQR=17-45) and IIA was 32.2 (IQR=11-70). The clinical phenotype was patch-only lesions in 160 patients (46.0%) significantly more often in stage IA/B (53.5% and 42.3%, respectively) than IIA (18.5%),  $P=0.002$ ; 52 patients (14.9%) had plaque-only lesions, 31/172 (18.0%) with stage IA, 18/149 (12.1%) patients with IB and 3/27 (11.1%) with IIA. The remaining 136 patients (39.1%) had co-existing patches and plaques. Other clinical features recorded included follicular lesions (24.4%), poikiloderma (15.2%) and hypopigmented lesions (8.0%).

Follicular lesions (clinical lesions of MF showing predilection for hair follicles and include follicular papules, plaques, alopecia, milia and cysts) were present in 85 patients, 67 met a diagnosis of folliculotropic MF, but follicular lesions also occur in classical MF. Follicular

lesions were less common in patients with IA (14.4%) than IB (32.2%) or IIA (26.0%) ( $P=0.009$ ); Whilst poikiloderma and hypopigmentation were found at a similar frequency in all stages ( $p=0.452$  and  $p=0.313$  respectively) but had a positive association with patches. 12(3.4%) patients had co-existing lymphomatoid papulosis lesions which is similar to previously reported<sup>15,16</sup>.

### **Skin Histology and Clonality**

From central pathology review 284 had classical MF (81.6%), 62 patients (17.8%) had folliculotropic MF (FMF) and 2 syringotropic MF (0.6%). The T-cell phenotype was CD4+ in 307 patients (88.2%). In the 41 with negatively staining CD4 tumour cells 34 were positive for CD8 and 7 double-negative (CD4-CD8-). In addition to CD4 positivity, 7 also had tumour cells staining for CD8 (CD4+CD8+ or double-positive). Six patients (1.7%) had LCT in the skin and 2 of these had FMF.

Not all sites perform T-cell receptor gene analysis in the skin. This was recorded in 205 patients and was clonal in 132 patients (64.4%) at a similar percentage in all stages ( $P=0.848$ ); 70/109 (64.2%) with stage IA, 46/73 (63.0%) with IB and 16/23 (69.6%) with IIA.

### **Haematological Parameters and Serum LDH**

B-classification data was available in 121/348 patients and was B0 in 96/121 patients (79.3%) and B1 in 25/121 patients (20.7%) (Table 2). By staging definition, no patients had B2 which is criteria for advanced-stage disease (IVA1 or higher). Of the 25 patients with B1 10/55 (18.2%) had IA, 12/46 (26.1%) IB and 3/21 (14.3%) IIA. Only 33.6% had TCR in blood tested and this was clonal in 8.5% (10 patients). Full blood count (FBC) and differential was tested in 68.7%. Lymphopenia was a frequent abnormality found in 10.3%, 1.7% had lymphocytosis.

LDH was recorded in 244/348 patients (70.1%) and was raised in 27 patients (11.1%) particularly in stage IIA (10/23, 43.5%) with respect to IA (8/120, 6.7%) and IB (9/101, 8.9%) ( $P<0.001$ ).

### **Lymph node involvement**

Radiological imaging was not mandatory for this study. It was performed in 143 patients (41.1%) and 23/143 patients (16.1%) had lymph node (LN) enlargement by CT criteria for MF defined as  $\geq 15$ mm in the greatest diameter (long-axis) by staging definition these patients are IIA. No patients had visceral disease which would be advanced stage (IVB).

Of the 23 patients with enlarged LN on imaging, 9 patients had enlarged nodes at 1 region, whilst the remaining had 2 or more (5 at 2, 4 at 3, 4 at 4 and 1 at 5+ regions). Mostly lymphadenopathy was found at peripheral sites; 69.5% inguino-femoral, 56.5% axillary and 21.7% cervical. Only 1 patient had centrally enlarged LN (1 abdominal). 6 patients had a LN biopsy; 4 classed as N1 (dermatopathic lymphadenopathy) and 2 as N2 (early nodal involvement)<sup>25</sup>. The remaining 21 stage IIA patients were recorded as Nx (4 with LN identified by clinical exam alone, no imaging/biopsy and 17 with LN identified on imaging without biopsy).

## **Discussion**

PROCLIP is a prototype data collection study for rare cancers. The PROCLIP database is an easily accessible secure web-based system with predefined datasets to allow prospective collection of international data. This unique database checks accuracy of information using in-built intelligence which auto-calculates stage, prevents entry of obscure data and disallows saving of incomplete data. In addition, a Data Monitoring Committee [Appendix I] annually trawls data for inaccuracies which are then raised as queries to Centres. Legal data sharing agreements allow anonymised international data share. An associated Federated Biobank registers tissue stored for future translational studies providing an invaluable resource of detailed clinicopathological/genotypic data linked to pre-treatment biobanked samples.

PROCLIP recruited a cohort of 430 patients suspected with early-stage MF in 3 years from 29 Centres in 15 countries spanning 5 continents. This unprecedented collaboration will test parameters recorded against survival to develop a prognostic index powered to identify early-stage MF patients at higher risk of disease progression.

Diagnosis of early-stage MF is complex<sup>2</sup>. Hence, all enrolled patients are subject to a rigorous clinicopathological review. Overall, the central review process was concordant with the diagnosis of early-stage MF in 85.5% of patients with most 'passing' on the initial 'Virtual Central Review' process. 41 patients had Real-Time review and the 'pass-rate' was 46.3%. Failure of central review was due to advanced-stage disease 3.9% and non-diagnostic in 10.6%. Interestingly, despite the strict criteria for passing central review, of those tested for T-cell clonality in skin (performed at individual sites not centrally) only 64.4% had identification of a T-cell skin clone with similar frequency in each stage  $P=0.848$ . Methodology most frequently included the Biomed 2 panel<sup>26</sup> with only one centre using high-throughput-sequencing (HTS) platforms<sup>27</sup>. The sensitivity of standard PCR (and subjective reading by gel electrophoresis) is less than clinically used HTS

platforms<sup>28</sup>. Results cannot be standardised given the heterogeneity of methods used regionally/locally. Thus, clonality alone is not a reliable sensitive diagnostic test.

There was a diagnostic delay in 85.6% of patients from onset of lesions to diagnosis of early MF in participating Centres with a median delay of 36 months (not including time for central review) highlighting the need for improved diagnostic tests in early-stage MF. Most patients presented with stage I (49.4%=IA, 42.8%=IB) but 7.8% presented with nodal enlargement (IIA). No difference in delay was noted between stages suggesting that stage IB-IIA are not late diagnosis of 'IA' patients. This could be interpreted that a delay does not result in progression of skin involvement (to a higher stage at least). Nonetheless, delay can be stressful for patients and has the potential to lead to inappropriate treatments. Indeed, at worst, misdiagnosis particularly when followed by inappropriate use of immunosuppressive therapy which may result in a more rapid disease progression<sup>29</sup>.

Most (81.6%) presented with classical MF and 17.8% with FMF ratified at central review. FMF has previously been associated with more aggressive disease and a prognosis more similar to tumour-stage disease<sup>7</sup>. However recent publications have shown a subgroup of FMF patients with early-stage disease with a good prognosis<sup>30-32</sup> and these patients will be tracked to determine the prognostic relevance of FMF in early-stage MF.

Distinguishing patches from plaques of MF is subjective but may determine treatment approaches in early-stage disease<sup>33-34</sup>. Benton et al 2013<sup>10</sup> found the presence of plaques to be an independent factor for poor survival in early-stage disease but an adverse outcome due to plaque lesions at diagnosis has not been shown in a prospective study. The revised 2007 staging guidelines doesn't include plaques as a determinant of stage but recommended recording the presence of patch only or patches/plaques ('a' for patches and 'b' for patches/plaques). 46.0% of our cohort presented with patch-only disease and 39.1% with patches/plaques. Plaques were seen in 46.5% with IA but were more frequent in IB disease (57.7%) P=0.045.

The majority of patients (97.1%) presented in good health with an ECOG score of 0. There was a male predominance with male:female ratio 1.7:1 and median age of presentation was 57 years (IQR=44-67) with no difference between stages. This is significantly younger than the median age of 64.5years (IQR=55-74) of the cohort of 1275 advanced-stage MF patients reported by our group (P<0.001)<sup>15</sup>. This retrospective analysis of advanced-stage MF found age>60years, LCT in skin, stage IV and raised LDH all to be independent factors with a worse prognosis<sup>12</sup> but the significance of these findings in early-stage MF is unknown. In this early cohort LCT was verified at central

review in 1.7% of cases. A raised serum LDH was found in 11.1% and was significantly raised in IIA (43.5%) compared to IA (6.7%) and IB (8.9%)  $P < 0.001$ .

Blood involvement in early-stage MF is part of the staging for MF and is utilised in the response criteria<sup>35,36</sup>. The majority of patients tested had no blood involvement (B0=79.3%) but B1 level blood involvement was found in 20.7% occurring in all stages. Lymphopaenia was a frequent haematologic abnormality in this cohort with early-stage MF (10.3%) and increased to 29.6% in IIA. It should be noted these tests are at diagnosis, so MF treatment is not the cause. Lymphopaenia is associated with immunosuppression which may reduce the innate immunity ability to keep cancers, or specifically MF, in check. Cyclosporin a potent suppressor of lymphocytes is known to precipitate more aggressive MF and is contraindicated<sup>6,29</sup>. The significance of blood abnormalities in early-MF is unknown and tracking these patients for survival will determine the relevance.

Radiological imaging is not a recommended investigation in early-stage MF unless there is clinical lymphadenopathy or type-B symptoms but nearly half of patients had an imaging scan (143 patients, 41.1%) although only 23/143 patients (16.1%) had enlarged LN.

PROCLIFI has collected a confirmed early-stage MF cohort who will be followed-up for survival to identify prognostic factors which may allow better management and improve survival by identifying patients at risk of progression. There is frequent diagnostic delay with a median of 36 months highlighting the difficulties in accurate diagnosis which is confounded by the lack of a singular diagnostic test and currently relies on clinical, pathological and genotypic studies. Tissue samples within the PROCLIFI federated biobank may be used for future translational studies which may identify biomarkers to aid diagnosis and to identify predictive and prognostic biomarkers and novel targets for therapy. This study design is a prototype which may be useful in other rare diseases.

#### **Legends:**

**Appendix I** – Skindex-29 quality-of-life questionnaire

**Appendix II** – Datasets Collected For PROCLIFI Study

**Appendix III** – Members of the Data Monitoring Committee (DMC)

**Appendix IV** – Central Review Process - methodology

**Figure 1** PROCLIFI Recruitment Plus Central Review Results per Centre

**Figure 2** Flow Diagram of Central Review Process and Results

**Table 1** Clinical data of 348 Early-Stage MF Patients

**Table 2** Haematologic Data of 348 Early-Stage MF Patients

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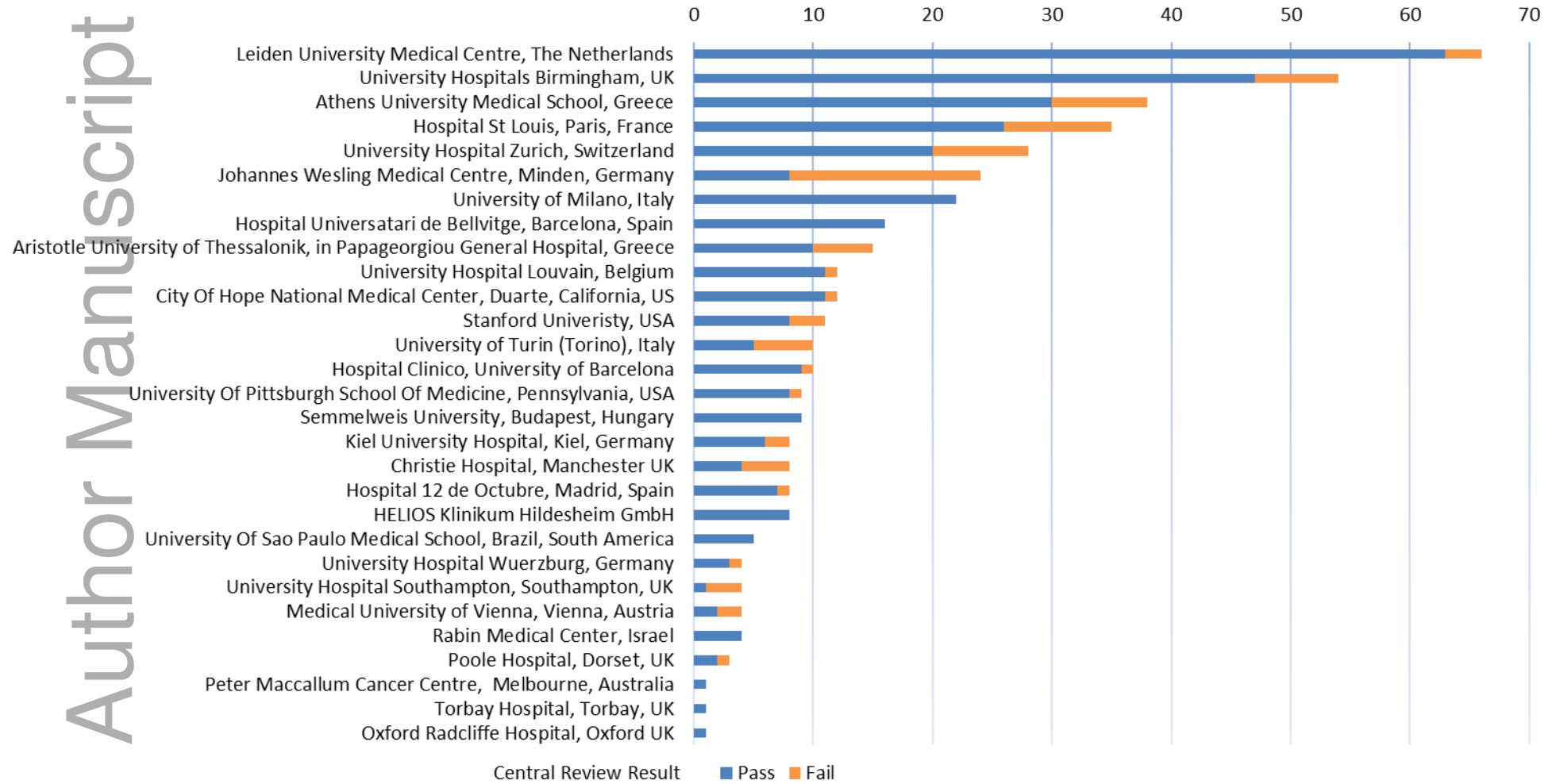
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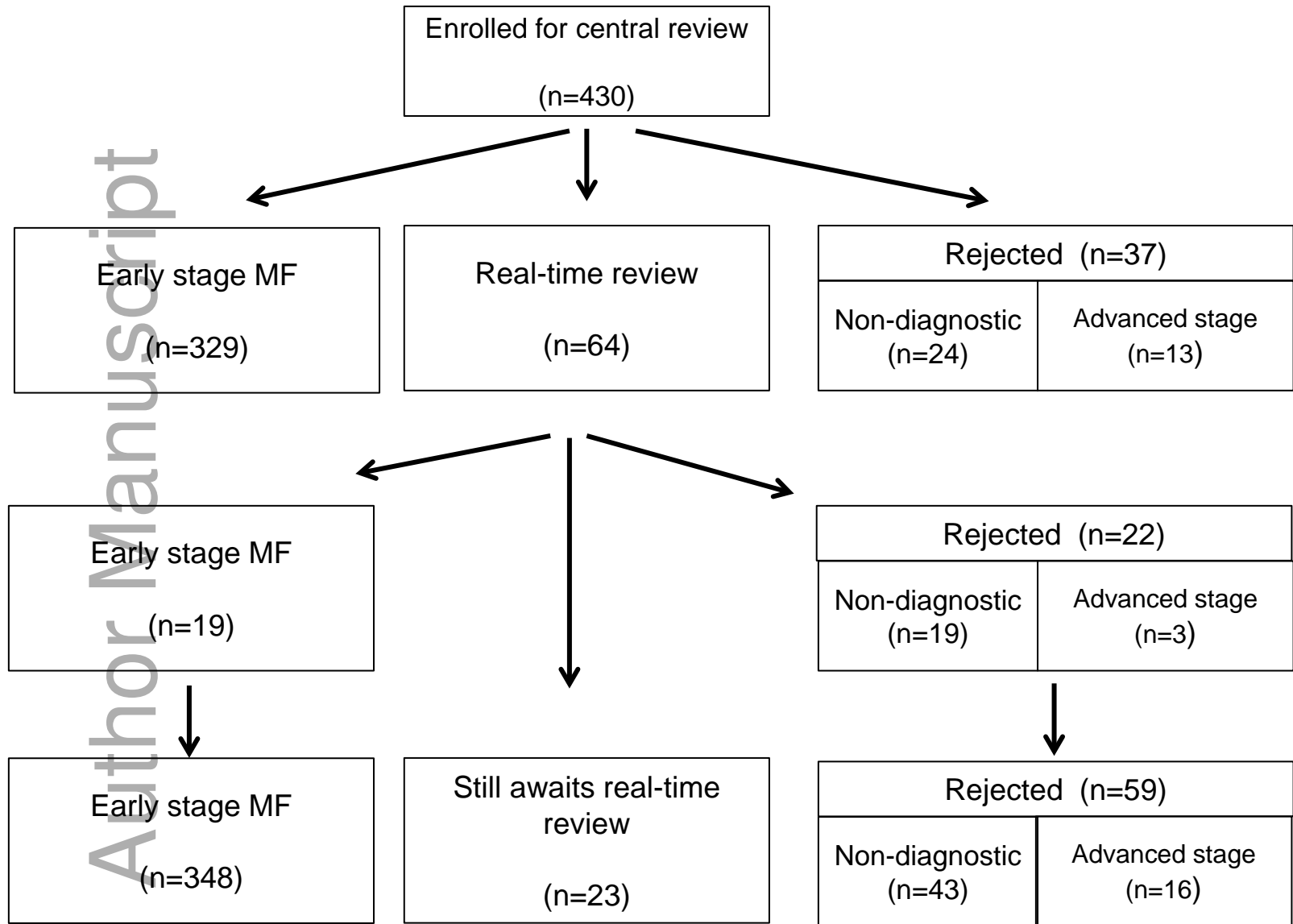
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Figure 1 Recruitment of Early Stage MF Patients to PROCLIFI by Centre with Central Review Results





**Figure 2. Flowchart showing results of virtual and real-time review processes**