International prognostic scoring system for mastocytosis (IPSM): a retrospective cohort study

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Summary

Background—The WHO classification separates mastocytosis into distinct variants, but prognostication remains a clinical challenge. The aim of this study was to improve prognostication for patients with mastocytosis.

Methods—We analysed data of the registry of the European Competence Network on Mastocytosis including 1639 patients (age 17–90 years) diagnosed with mastocytosis according to

WHO criteria between Jan 12, 1978, and March 16, 2017. Univariate and multivariate analyses with Cox regression were applied to identify prognostic variables predicting survival outcomes and to establish a prognostic score. We validated this International Prognostic Scoring System in Mastocytosis (IPSM) with data of 462 patients (age 17–79 years) from the Spanish network Red Española de Mastocitosis diagnosed between Jan 22, 1998, and Nov 2, 2017.

Findings—The prognostic value of the WHO classification was confirmed in our study (p<0·0001). For patients with non-advanced mastocytosis (n=1380), we identified age 60 years or older (HR 10·75, 95% CI 5·68–20·32) and a concentration of alkaline phosphatase 100 U/L or higher (2·91, 1·60–5·30) as additional independent prognostic variables for overall survival. The resulting scoring system divided patients with non-advanced mastocytosis into three groups: low (no risk factors), intermediate 1 (one risk factor), and intermediate 2 (two risk factors). Overall survival and progression-free survival differed significantly among these groups (p<0·0001). In patients with advanced mastocytosis (n=259), age 60 years or older (HR 2·14, 95% CI 1·42–3·22), a concentration of tryptase 125 ng/mL or higher (1·81, 1·20–2·75), a leukocyte count of 16×10^9 per L or higher (1·88, 1·27–2·79), haemoglobin of 11 g/dL or lower (1·71, 1·13–2·57), a platelet count of 100×10^9 per L or lower (1·63, 1·13–2·34), and skin involvement (0·46, 0·30–0·69) were prognostic variables. Based on these variables, a separate score for advanced mastocytosis with four risk categories was established, with significantly different outcomes for overall survival and progression-free survival (p<0·0001). The prognostic value of both scores was confirmed in 413 patients with non-advanced disease and 49 with advanced mastocytosis from the validation cohort.

Interpretation—The IPSM scores for patients with non-advanced and advanced mastocytosis can be used to predict survival outcomes and guide treatment decisions. However, the predictive value of the IPSM needs to be confirmed in forthcoming trials.

Introduction

The term mastocytosis denotes a heterogeneous group of disorders characterised by abnormal expansion and accumulation of mast cells in various organs. The estimated prevalence of systemic mastocytosis is one case in 10 000 adults, and the estimated incidence amounts to one new case per 100 000 people per year.[1] A diagnosis of mastocytosis is based on criteria provided by WHO.[2,3] The WHO classification includes several prognostic variables and represents a well-established diagnostic method with prognostic effect. However, prognosis and survival outcomes of patients vary substantially among cases, even within WHO entities,[4,5] and prediction of the clinical course and survival outcomes in individual patients is difficult. Based on the WHO classification, mastocytosis can essentially be split into non-advanced disease and advanced systemic disease.[2, 3] Non-advanced mastocytosis includes patients with cutaneous mastocytosis, indolent systemic mastocytosis, and smouldering systemic mastocytosis. These patients usually have a stable clinical course and a good prognosis.[4] By contrast, advanced systemic mastocytosis includes

patients with aggressive systemic mastocytosis, systemic mastocytosis with an associated haematological neoplasm, and mast cell leukaemia. These patients have a poor prognosis. [4, 6–9] Awareness of differences in disease biology and prognosis of patients with non-advanced mastocytosis and advanced systemic mastocytosis is important.

During the past two decades, several clinical, serological, cytomorphological, immunological, and molecular variables have been reported to be of prognostic significance in mastocytosis.[10–19] Several of these variables have been included in the WHO classification, such as organomegaly or cytopenias.[2,3] Other adverse prognostic variables include absence of skin lesions, multilineage involvement with *KIT* Asp816Val, mutations in genes other than *KIT* (eg, *SRSF2*, *ASXL1*, or *RUNX1*), increased amounts of β$_2$-microglobulin in serum, and raised amounts of alkaline phosphatase.[10,12–19] However, these variables were studied in smaller patients' cohorts and without comparing all potential risk factors with each other in multivariate analyses. Moreover, several of these variables (eg, molecular profiling) are not available at all centres.

Several attempts have been made to improve prognostication of mastocytosis by establishing scoring systems.[13,20,21] However, currently available scores are based on a limited number of patients and have not been validated in independent cohorts. More importantly, current scoring systems do not address the point that non-advanced mastocytosis and advanced systemic mastocytosis are completely different disease groups with divergent disease biology and distinct patterns of prognostic factors.[13,20,21]

Although the WHO classification is a well-established diagnostic approach with prognostic effect, advanced methods for prognostication in mastocytosis are scarce. The aim of this study was to confirm the prognostic effect of individual disease features and laboratory variables in patients with mastocytosis. Using data from the registry of the European Competence Network on Mastocytosis (ECNM), we identified the most discriminative prognostic variables and established a scoring system for use in daily practice. We also aimed to confirm the strength and effect of our scoring system in an independent validation cohort.

Methods

Study design and participants

Our study was retrospective in design and comprised two datasets, a test cohort and a validation cohort. We obtained data for the test cohort from the ECNM registry. We included patients with mastocytosis as per WHO criteria diagnosed between Jan 12, 1978, and March 16, 2017, at 22 centres in Europe and one US centre (Stanford; appendix p 25).[6] We excluded patients who had less than 2 days of follow-up data. The ECNM registry was approved by ethics committees of the participating centres. Details about the ECNM registry, study design, eligibility, inclusion criteria, age limits, disease categories, ethics approval, informed consent, and prognostic variables are provided in the appendix (pp 2–5).

We obtained data for the validation cohort from the Spanish network Red Española de Mastocitosis (REMA). This cohort includes patients with mastocytosis as per WHO criteria

diagnosed between Jan 22, 1998, and Nov 2, 2017 (appendix pp 5, 32). The REMA registry was approved by the ethics committees of the participating centres. In the REMA cohort, the following patients were excluded: patients with well-differentiated non-advanced systemic mastocytosis, patients with cutaneous mastocytosis but no bone marrow data, individuals with non-advanced systemic mastocytosis and less than 12 months of follow-up data, and patients with not enough data for analyses.

We excluded from the analysis of prognostic factors children (aged <17 years) with cutaneous mastocytosis because no bone marrow studies were available for most patients and because of the different disease biology of this group (in most patients, no *KIT* Asp816Val mutation is found). We also excluded patients with mast cell sarcoma because of the rarity of the disease and its unique pathology and pathogenesis (usually *KIT* Asp816Val is not detectable in mast cell sarcoma).

Procedures

We obtained clinical and laboratory data from both registries taken at diagnosis and during follow-up (appendix pp 26–29) in patients with indolent systemic mastocytosis, cutaneous mastocytosis (both children [aged <17 years] and adults [aged 17 years]), systemic mastocytosis with an associated haematological neoplasm, aggressive systemic mastocytosis, smouldering systemic mastocytosis, mast cell leukaemia, and mast cell sarcoma. Data were obtained retrospectively by chart review in the ECNM and REMA registries and were controlled regularly, with data clearing and updated follow-up once a year. We extracted data for survival outcomes and for variables to be considered as potential prognostic factors for development of the score. Details about development of the score and its validation are described in the appendix (p 6). In brief, only variables recorded in at least 70% of patients were included. Based on results of the statistical evaluation (including univariate and multivariate Cox regression), we established the scores for patients with non-advanced mastocytosis and advanced systemic mastocytosis.

Statistical analysis

We retrospectively analysed overall survival (time from diagnosis to death from any cause), progression-free survival (time from diagnosis to disease progression, defined as a shift from a low-risk disease category to a higher risk category), and event-free survival (time from diagnosis to progression or death, whichever occurred first) according to the Kaplan-Meier method with Mantel-Cox tests for group comparisons. Progression was defined as a shift from a lower risk to a higher risk category of mastocytosis. Moreover, development of an associated haematological neoplasm as well as the transformation of such an associated haematological neoplasm into a higher grade of disease (eg, from a lower grade myeloid malignancy such as myelodysplastic syndrome to acute myeloid leukaemia) counted as progression. Since mast cell leukaemia is an end-stage disease (no further progression can occur) and mastocytosis in the skin is a provisional diagnosis for patients with skin involvement but unknown or unavailable bone marrow, these two patient groups were excluded from the analysis of progression-free survival.

We applied univariate Cox regression for all potentially prognostic variables. All variables that showed prognostic significance in univariate analyses were included in multivariate analyses. These analyses were done separately for patients with non-advanced mastocytosis (excluding children with cutaneous mastocytosis) and those with advanced systemic mastocytosis. We checked the proportional hazard assumption by testing the interaction to define whether the hazards of prognostic factors change during follow-up (depending on survival time reached).

Based on results obtained in multivariate analyses, we developed two prognostic scoring systems, one for patients with non-advanced mastocytosis and one for those with advanced systemic mastocytosis.

All statistical analyses were done using GraphPad Prism version 6 (GraphPad Software, San Diego, CA, USA) and Stata version 13.1 (StataCorp, College Station, TX, USA).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to the ECNM dataset and IA-T and AO had full access to the REMA dataset. The corresponding author had final responsibility for the decision to submit for publication.

Results

Between Jan 12, 1978, and Mar 16, 2017, 2361 patients were enrolled in the ECNM registry, of whom 567 were excluded because they were not followed up for long enough (figure 1). 1794 patients had at least 2 days of follow-up data available in the ECNM registry and comprised the test cohort. Median age at diagnosis was 46 years (range 0·15–90). Among the test cohort, 1006 had indolent systemic mastocytosis, 280 had cutaneous mastocytosis (153 children and 127 adults), 174 had systemic mastocytosis with an associated haematological neoplasm, 62 had aggressive systemic mastocytosis, 53 had smouldering systemic mastocytosis, 23 had mast cell leukaemia, and two had mast cell sarcoma. A further 194 adults had typical mast cell infiltrates in the skin, but no bone marrow examination was done (table 1; appendix pp 30, 31).

Between Jan 22, 1998, and Nov 2, 2017, 1997 patients were collected in the REMA registry. 1535 individuals were excluded from our analyses (figure 1); thus, the validation cohort consisted of 462 patients. Median age at diagnosis was 47 years (range 17–79). 384 patients had indolent systemic mastocytosis, 25 had systemic mastocytosis with an associated haematological neoplasm, 19 had aggressive systemic mastocytosis, 18 had cutaneous mastocytosis, 11 had smouldering systemic mastocytosis, and five had mast cell leukaemia (table 1; appendix pp 5, 32).

Median follow-up in the ECNM registry was 3·4 years (IQR 1·4–6·6; appendix pp 7, 9). The data obtained in our registry confirmed that the WHO classification defines two prognostic groups: non-advanced mastocytosis and advanced systemic mastocytosis. The non-advanced mastocytosis category comprised patients with cutaneous mastocytosis, mastocytosis in the

skin, indolent systemic mastocytosis, and smouldering systemic mastocytosis. The advanced systemic mastocytosis category consisted of patients with aggressive systemic mastocytosis, mast cell leukaemia, mast cell sarcoma, and systemic mastocytosis with an associated haematological neoplasm.

In the total cohort, median overall survival was 28·4 years (95% CI 19·5–37·0) and 10-year overall survival was 81·9% (95% CI 7·7–84·7). Differences in overall survival between WHO cohorts were significant (p<0·0001). Patients in the non-advanced mastocytosis category had improved prognosis compared with patients with advanced systemic mastocytosis (figure 2). However, subtle differences in overall survival were noted among patients with non-advanced mastocytosis. For example, individuals with cutaneous mastocytosis (both children and adults) had improved overall survival compared with all other subgroups, including patients with indolent systemic mastocytosis (figure 2A). No substantial differences were noted in overall survival when comparing cutaneous mastocytosis in children (n=153) and adults (n=127; appendix p 10). In patients with indolent systemic mastocytosis (73% with skin lesions; appendix p 30), 10-year overall survival was 93·5% (95% CI 90·1–95·8) and median overall survival was 28·4 years (95% CI 24·1–32·8). 10-year overall survival was 100% for patients with cutaneous mastocytosis, 92·5% (85·9–96·0) for those with mastocytosis in the skin, and 84·5% (61·1–84·5) for individuals with smouldering systemic mastocytosis, but median overall survival was not reached in these subgroups. Median overall survival was 5·7 years (95% CI 0·6–4·5) for patients with aggressive systemic mastocytosis, 1·9 years (0·0–5·2) for those with mast cell leukaemia, 1·1 years for one patient with mast cell sarcoma, and 2·9 years (2·5–3·3) for individuals with systemic mastocytosis with an associated haematological neoplasm (figure 2A). 10-year overall survival was 44·0% (95% CI 26·6–60·1) in patients with aggressive systemic mastocytosis, 29·9% (10·0–53·2) in those with mast cell leukaemia, 0% for mast cell sarcoma, and 11·2% (7·5–12·1) for individuals with systemic mastocytosis with an associated haematological neoplasm. In 11 (22%) of 49 patients with non-advanced mastocytosis and 109 (75%) of 145 patients with advanced systemic mastocytosis, the cause of death was related to mastocytosis (appendix pp 7, 33).

Progression-free survival was analysed in 1577 (88%) patients after excluding patients with mastocytosis in the skin (n=194) and mast cell leukaemia (n=23). Progression of disease was observed in 88 (6%) of 1577 patients, including 39 (4%) of 1006 patients with indolent systemic mastocytosis, five (9%) of 53 with smouldering systemic mastocytosis, 11 (18%) of 62 with aggressive systemic mastocytosis, and 27 (16%) of 174 with systemic mastocytosis with an associated haematological neoplasm (table 1, appendix p 34). Six (2%) of 280 patients with cutaneous mastocytosis developed indolent systemic mastocytosis (one [1%] of 153 children and five [4%] of 127 adults; appendix p 34). In 32 (2%) of 1339 patients with non-advanced mastocytosis, progression to advanced systemic mastocytosis was seen in 27 (3%) of 1006 patients with indolent systemic mastocytosis and five (9%) of 53 patients with smouldering systemic mastocytosis (table 1, appendix pp 34, 35). Among 194 patients with mastocytosis in the skin, 49 had a bone marrow examination during follow-up, resulting in a diagnosis of cutaneous mastocytosis in 16 patients, indolent systemic mastocytosis in 30, smouldering systemic mastocytosis in one, aggressive systemic mastocytosis in one, and systemic mastocytosis with an associated haematological neoplasm

in one (appendix p 36). For all patients, progression-free survival at 10 years was 88·0% (95% CI 85·8–91·5; appendix p 9). Differences in progression-free survival between WHO cohorts were significant (p<0·0001). None of the WHO groups reached median progression-free survival during the study (figure 2B). Significant differences between WHO groups were also seen for event-free survival (p<0·0001; appendix pp 7, 11). Overall survival and progression-free survival in patients with systemic mastocytosis with an associated haematological neoplasm, according to subtype of neoplasm, are shown in the appendix (p 12).

In patients with indolent systemic mastocytosis or smouldering systemic mastocytosis, alkaline phosphatase of 100 U/L or higher was associated with a significantly increased risk of disease progression to advanced systemic mastocytosis (appendix p 37). Age 60 years or older (HR 4·90, 95% CI 2·51–9·40) and alkaline phosphatase of 100 U/L or higher (2·10, 1·07–4·05) were identified as significant (independent) predictors of evolution to higher grade mastocytosis in patients with non-advanced systemic mastocytosis; these same variables were also predictive of overall survival (HR 10·75, 95% CI 5·68–20·32; and 2·91, 1·60–5·30, respectively; table 2). Based on these variables, we established a simple score, the International Prognostic Scoring System for Mastocytosis (IPSM), and applied it in 1058 of 1380 patients with non-advanced mastocytosis in whom data for all relevant prognostic variables were available. Patients with non-advanced mastocytosis without additional risk factors comprised the low-risk group (median age 43 years), and those with one or two risk factors formed the intermediate-risk group 1 (referred to as int-1; median age 56 years) and intermediate risk-group 2 (referred to as int-2; median age 64 years), respectively.

Overall survival at 10 years was 98·1% (95% CI 95·2–99·3) in the low-risk group, 87·1% (77·2–91·9) in the int-1 group, 52·1% (29·4–70·7) in the int-2-risk group, and 22·0% (13·9–21·2) in patients with advanced systemic mastocytosis (p<0·0001; figure 3A). Significant differences were also observed in progression-free survival at 10 years: 96·3% (95% CI 92·2–98·3) in lowrisk patients, 86·7% (77·9–92·2) in int-1 patients, 76·3% (52·2–89·4) in int-2 patients, and 61·1% (42·0–75·6) in patients with advanced systemic mastocytosis (figure 3B). The significance of the score was also confirmed for overall survival in mastocytosis in the skin and indolent systemic mastocytosis (p<0·0001) and for progression-free survival in cutaneous mastocytosis (p<0·0001), indolent systemic mastocytosis (p=0·0006), and smouldering systemic mastocytosis (p=0·0011; appendix pp 13, 14). In patients with smouldering systemic mastocytosis, the differences in overall survival were not significant (p=0·093), which might be attributable to the relatively low number of patients with this disorder. The score was also of prognostic significance regarding event-free survival in all subgroups (appendix pp 8, 15, 16).

In patients with advanced systemic mastocytosis, age 60 years or older (HR 2·14, 95% CI 1·42–3·22), tryptase 125 ng/mL or higher (1·81, 1·20–2·75), leukocytes 16×10^9 per L or higher (1·88, 1·27–2·79), haemoglobin 11 g/dL or lower (1·71, 1·13–2·57) platelets 100×10^9 per L or lower (1·63, 1·13–2·34), and skin involvement (0·46, 0·30–0·69) were independent prognostic factors for overall survival in multivariate analyses (table 2). These variables were used to optimise scoring in patients with advanced systemic mastocytosis. The score was applied in 229 (88%) of 259 patients for whom data for all variables were

available. Every risk factor with an HR greater than 1·50 scored 1 point, and risk factors with an HR of 0·50 or lower scored –1 point. By adding all risk points, four different risk groups were established. Patients with scores from –1 to 0 points (no risk factors) were grouped in advanced systemic mastocytosis 1 (referred to as AdvSM-1), those with a score of 1 point (one risk factor) were in the advanced systemic mastocytosis 2 (AdvSM-2) group, individuals with scores of 2–3 points (two or three risk factors) were grouped in advanced systemic mastocytosis 3 (AdvSM-3), and patients with a score of 4 or 5 points (four or five risk factors) were included in the advanced systemic mastocytosis 4 (AdvSM-4) group.

These groupings were of prognostic significance for overall survival (p<0·0001; figure 3C). Overall survival of patients in risk groups AdvSM-1 and AdvSM-2 was similar to that of patients with non-advanced mastocytosis in the int-1 and int-2 risk groups, respectively (figure 3C). The significance of the score for advanced systemic mastocytosis was also confirmed for progression-free survival and event-free survival (p<0·0001; figure 3D; appendix p 17) and for the individual WHO entities of aggressive systemic mastocytosis, mast cell leukaemia, and systemic mastocytosis with an associated haematological neoplasm (appendix pp 18–20).

The IPSM was validated using data from the REMA registry for 413 (89%) patients with non-advanced mastocytosis and 49 (11%) with advanced systemic mastocytosis. Both scores showed significant results in the validation sample (p<0·0001 for overall survival, p<0·0001 for progression-free survival, and p<0·0001 for event-free survival), confirming the prognostic value and usefulness of the IPSM (appendix pp 21–23).

Discussion

Using data from a large cohort of patients in the ECNM registry, we identified independent prognostic variables for patients with non-advanced mastocytosis (age and alkaline phosphatase) and advanced systemic mastocytosis (tryptase, blood counts, and absence of skin involvement). Based on these variables, we established a simple prognostic score system, referred to as IPSM. The predictive value of this new score was confirmed in an independent validation cohort provided by the REMA.

So far, it remains unknown whether adults with cutaneous mastocytosis have a favourable outcome compared to patients with indolent systemic mastocytosis. In our study, patients with adulthood cutaneous mastocytosis had good overall survival, which was similar to that recorded in children with cutaneous mastocytosis and improved compared with overall survival of patients with indolent systemic mastocytosis or mastocytosis in the skin. The improved overall survival seen in children and adults with cutaneous mastocytosis could be explained by the lower numbers of cases with disease progression. Patients with mastocytosis in the skin and indolent systemic mastocytosis had similar overall survival, suggesting that most patients with mastocytosis in the skin might indeed suffer from indolent systemic mastocytosis, whereas adults with cutaneous mastocytosis have a better prognosis. So far, it remains unknown why adults with cutaneous mastocytosis have a better overall survival compared to patients with indolent systemic mastocytosis or mastocytosis in the skin. One explanation could be that indolent systemic mastocytosis is a more advanced

disease with higher risk of progression to advanced systemic mastocytosis. An alternative explanation could be the higher median age of patients with mastocytosis in the skin (age 43 years) and indolent systemic mastocytosis (age 47 years) compared to adults with cutaneous mastocytosis (age 37 years).

Several clinical and laboratory parameters are prognostic variables for mastocytosis.[7,10,12–19] In our study, amounts of alkaline phosphatase 100 U/L or higher and age 60 years or older were the two major independent predictors of survival in patients with non-advanced mastocytosis and were used to establish the IPSM. Alkaline phosphatase has already been shown to be of prognostic value in systemic mastocytosis in previous studies.[12,13,20] A rise in the amount of alkaline phosphatase could reflect mastocytosis-mediated organ damage in the bones, liver, or both.[13,20] High amounts of alkaline phosphatase found in some patients with non-advanced mastocytosis might, therefore, indicate clinically silent organ involvement. Such occult organ involvement could produce raised amounts of alkaline phosphatase even before the disease progresses to advanced systemic mastocytosis. Indeed, we found significantly more progressions in indolent or smouldering systemic mastocytosis to advanced systemic mastocytosis in patients with amounts of alkaline phosphatase of 100 U/L or higher. Surprisingly, in patients with advanced systemic mastocytosis, alkaline phosphatase was not of prognostic value, contrasting with findings of previous studies.[13,20–22] However, in previous studies, the prognostic value of alkaline phosphatase was examined in the overall cohort of patients with non-advanced mastocytosis and advanced systemic mastocytosis,[20,21] whereas in our study, patients with non-advanced mastocytosis and advanced systemic mastocytosis were analysed separately. Amounts of alkaline phosphatase might also fluctuate over time in individual patients, which could represent a limitation of this variable. However, a constantly increasing amount of alkaline phosphatase must raise suspicion of disease progression.

Analysing the median age of our patients, we saw that low-risk patients were younger (age 43 years) than patients in the int-1 group (age 56 years) and the int-2 group (age 64 years). A simple explanation for this observation could be that reduced life expectancy is mainly attributable to the older age of these patients. However, not only overall survival but also progression-free survival significantly differed among these patients. Thus, our results cannot only be accounted for by differences in the natural age-dependent life expectancy. With respect to progression-free survival, increased clonal instability in advanced age might contribute to higher progression rates. Indeed, the number of mutations in haemopoietic stem cells increases with age.[23]

Organomegaly has been shown to be of prognostic importance in systemic mastocytosis.[13,20] In our study, organomegaly was not an independent prognostic factor for overall survival, which could be accounted for by the fact that organomegaly is represented in the WHO classification as either a B finding (ie, without organ damage) or as a C finding (ie, with organ damage caused by neoplastic mast cell infiltration).[2,3]

Patients with advanced systemic mastocytosis sometimes do not have skin involvement.[2,3] In our study, the absence of skin lesions was of prognostic importance in the multivariate analysis of patients with advanced systemic mastocytosis, but not in the multivariate analysis

of patients with non-advanced mastocytosis. This result has several explanations. First, it is well known that skin lesions are preferentially absent in patients with rapidly progressive aggressive systemic mastocytosis and mast cell leukaemia. Second, a subgroup of patients with indolent systemic mastocytosis have no skin lesions and their clinical course remains stable. Contrasting patients with advanced systemic mastocytosis, individuals with indolent systemic mastocytosis without skin lesions have a low mast cell burden and a favourable prognosis and are currently classified as isolated bone marrow mastocytosis as per the WHO classification.[2,3]

In patients with advanced systemic mastocytosis, disease biology and predictive variables are different from those of patients with non-advanced mastocytosis. Therefore, we analysed the effect of potential prognostic factors in patients with advanced systemic mastocytosis separately. Again, age was of prognostic importance. Other prognostic independent variables in patients with advanced systemic mastocytosis included elevated tryptase, abnormal blood counts, and absence of skin involvement. Using these variables, patients with advanced systemic mastocytosis were split into four risk groups, with significant differences with respect to overall survival, event-free survival, and progression-free survival. The prognosis of patients in the int-1 and int-2 risk groups overlapped with that of patients in the AdvSM-1 and AdvSM-2 groups, respectively. This observation supports the strengths and clinical relevance of the IPSM. Thus, the IPSM might identify patients at higher risk than expected by WHO classification.

Several attempts have been made to develop prognostic scoring systems in mastocytosis.[13,20,21] However, these scores have limitations. First, most score studies have included relatively low numbers of patients and no validation cohort.[13,20,21] Second, most of these studies did not take the different disease biology of non-advanced mastocytosis and advanced systemic mastocytosis into account. Moreover, these score models are based on datasets that include more than 50% of patients with advanced systemic mastocytosis, whereas in our cohort only 15% of all patients had advanced systemic mastocytosis, which is closer to the real-life situation (appendix p 39).[13,20,21] The strength of the IPSM is that it is based on an unbiased statistical approach in more than 1000 patients, including all WHO variants of systemic mastocytosis at frequencies seen in daily practice. Moreover, prognostic factors were ascertained separately in patients with non-advanced mastocytosis and advanced systemic mastocytosis to establish optimal scoring models for both cohorts. Finally, our score was validated by an independent cohort from the REMA registry. The fact that the ECNM registry contains patients from many different centres and, thus, all categories of the disease in a rather balanced form also supports the strength of the IPSM. The IPSM incorporates the WHO classification and a few other simple variables, which provides a practicable method ready for use in patients with non-advanced mastocytosis and advanced systemic mastocytosis.

Other prognostic variables have been analysed previously in patients with systemic mastocytosis. Elevated β_2-microglobulin, multilineage involvement, the *KIT* Asp816Val allele burden, and mutations in additional genes are of prognostic importance.[13–16,24] Some of these markers, including β_2-microglobulin or multilineage involvement, are not measured in daily practice in most centres, as confirmed by our study. Moreover, *KIT* Asp816Val is

often analysed by conventional PCR but not by quantitative PCR. Other molecular markers were only available for a few patients in the ECNM registry, which shows that their use is still restricted to specialised centres. Moreover, molecular abnormalities are preferentially detected in patients who have advanced systemic mastocytosis, such as systemic mastocytosis with an associated haematological neoplasm, and are, therefore, not always WHO-independent variables. Finally, no standardised methodology for mutation analysis in mastocytosis is available to date. Nevertheless, such additional variables, and multilineage involvement, will soon be standardised and could support prognostication in the future.

In patients with non-advanced mastocytosis, progression to high-risk mastocytosis is a rare event and quality of life is most important and probably the key variable to look at when planning treatment.[25,26] Indeed, most patients die from causes other than mastocytosis. However, it is important to identify those few cases who are at risk to progress after some time. Since patients with non-advanced mastocytosis in the int-1 or int-2 risk groups have a higher risk of progression to advanced systemic mastocytosis, these patients need to be monitored closely to detect progression and to define the right time for intervention.

Considering the availability of new disease-modifying approaches in advanced systemic mastocytosis, our score could be important for making treatment decisions in daily practice: first, the WHO-based diagnosis is established and, second, our score is applied. Patients with advanced systemic mastocytosis usually need cytoreductive treatment, but the exact type of treatment depends on patient-related factors, disease aggressiveness, and the presence or type of associated haematological neoplasm.[27] At present, therapeutic options for slowly progressing advanced systemic mastocytosis include (offlabel) interferon alfa, cladribine, and midostaurin, which was approved for use by the US Food and Drug Administration and the European Medicines Agency in advanced systemic mastocytosis in 2017.[27–29] By contrast, in patients with advanced systemic mastocytosis with rapid progression or mast cell leukaemia, polychemotherapy and, if possible, haemopoietic stem-cell transplantation are considered.[30] However, the disease-modifying or curative potential of treatment has to be weighed against side-effects, and the IPSM might help with patients' selection. For example, in older patients with slowly progressing advanced systemic mastocytosis in a low-risk group according to the IPSM, treatment with midostaurin or cladribine could be a reasonable option.[29]

Our study has several limitations. Because of the retrospective nature of data collection, only variables used in daily routine are regularly captured. Likewise, we cannot exclude that other markers (eg, β_2-microglobulin, which was only available in 21% of all patients) would have added to prognostication when examined in all individuals and included in a scoring system. Moreover, patients are usually added to registries over a prolonged period, and diagnostic assays, standards, and sensitivity of molecular tests can change. Further, standards of clinical assessment and staging can change and might lead to earlier disease detection. For example, in patients with non-advanced mastocytosis, a diagnostic delay was sometimes suspected because first symptoms are reported by patients long before a diagnosis is established. In some patients, the initial diagnosis might have been cutaneous mastocytosis but, because of delay, the patient already had indolent systemic mastocytosis when diagnosed. However, it is almost impossible to prove that self-reported symptoms are related to mastocytosis. In the

ECNM registry, data were entered in a standardised way in a central web-based registry and were checked regularly for correctness and plausibility. To guarantee data quality, a yearly data-clearing process was done. Thus, our score is based on a robust and representative database.

In summary, the IPSM can optimise prognostication of patients with non-advanced and advanced systemic mastocytosis to better guide future interventions in these patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Research in context

Evidence before the study

We searched PubMed for articles published before June 7, 2019, containing information about individual prognostic variables and scoring systems established in mastocytosis. We did not restrict our search by language or type of article. Prognostication in mastocytosis is based mainly on the WHO classification.

Several prognostic variables have been identified, including absence of skin lesions, multilineage involvement with *KIT* Asp816Val, mutations in genes other than *KIT*, raised amounts of β_2-microglobulin in serum, or increased alkaline phosphatase. However, these variables have only been validated in a limited number of patients and only a few prognostic scoring systems are available. The Mayo score includes the WHO classification, age, platelet count, anaemia, alkaline phosphatase, and somatic mutations as major prognostic variables. Similar variables were identified and used in the Mannheim score. The Mayo and Mannheim scoring systems are based on a limited number of cases and have not been validated in independent cohorts so far. Previous prediction models have not addressed the important point that patients with non-advanced systemic mastocytosis and advanced systemic mastocytosis are subgroups of disease with completely different biology, disease course, survival outcomes, and patterns of prognostic factors.

Added value of this study

We established a new score, termed the International Prognostic Scoring System for Mastocytosis (IPSM), that was optimised for prognostication in patients with non-advanced mastocytosis and advanced systemic mastocytosis. This new score improves prognostication when compared with the WHO classification and other scoring models. Validation of our score by an independent sample-cohort confirmed its prognostic value.

Implications of all the available evidence

Several clinical studies have analysed the importance of prognostic variables in patients with mastocytosis, and attempts have been made to develop a multiparametric scoring system in this disease. In these scores, multilineage involvement of leukocytes with *KIT* Asp816Val, the *KIT* Asp816Val allele burden, or mutations in additional genes were included as prognostic variables. However, such markers are only available in a few specialised centres. Moreover, multilineage involvement and additional molecular abnormalities are preferentially detected in patients who have advanced systemic mastocytosis; thus, the contribution of these variables is limited. We based our new scoring system on simple variables that are checked regularly in daily practice. The resulting score (IPSM) is a useful and practicable method to identify patients with a higher risk of progression or death than would have been expected from the WHO classification. As our score is simple and ready for use, it should add substantially to management and patients' selection for various treatments in daily practice.
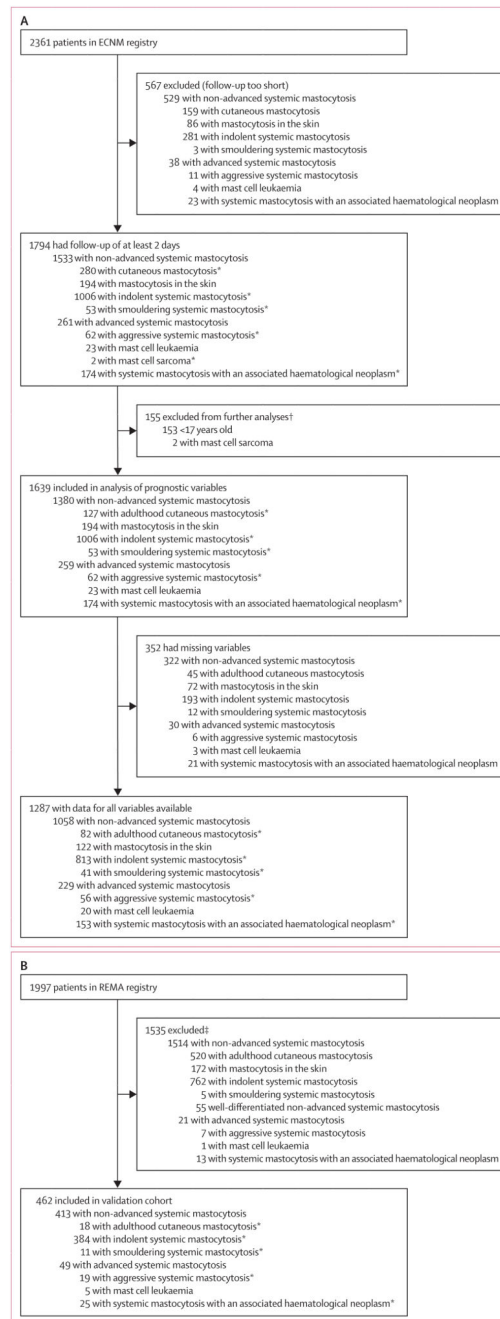
Figure 1. Study profile

Patients were selected from the ECNM registry (A) and REMA (B). In the ECNM cohort, only patients with at least 2 days of follow-up were included. All patients were included in analyses of overall survival and event-free survival. ECNM=European Competence Network on Mastocytosis. REMA=Red Española de Mastocitosis. *Included in analyses of progression-free survival. †Children (aged <17 years) were excluded from the assessment of prognostic factors and development of the score because, for most children, no bone marrow studies were available and because the disease is different. Patients with mast cell sarcoma

were excluded because of the rarity of the disease and its unique pathology and pathogenesis. ‡Those excluded were children (aged <17 years), had cutaneous mastocytosis without a bone marrow study, had less than 12 months of follow-up for non-advanced systemic mastocytosis, or did not have enough data.
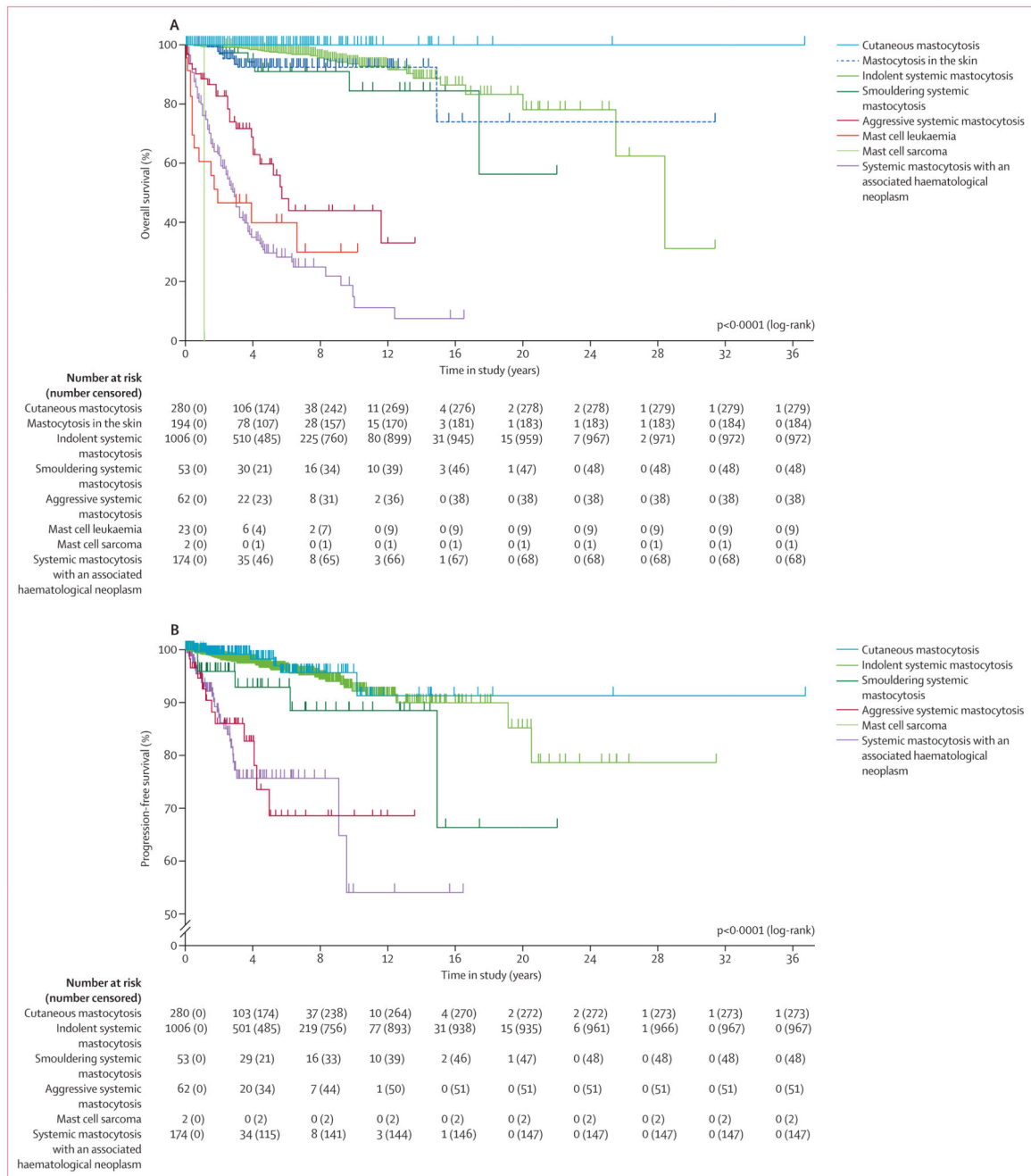
Figure 2. Survival outcomes in WHO subgroups of mastocytosis

Kaplan–Meier curves show the probability of overall survival (A) and progression-free survival (B) in subgroups of patients with mastocytosis, defined by WHO criteria.

A

Overall survival (%)

p<0·0001 (log-rank)

B

Progression-free survival (%)

p<0·0001 (log-rank)

Key for A and B
- Low
- Int-1
- Int-2
- AdvSM

Number at risk (number censored)

Low	711 (0)	351 (356)	149 (556)	55 (650)	20 (685)	9 (696)	5 (700)	2 (702)	0 (703)
Int-1	299 (0)	144 (147)	63 (299)	30 (251)	9 (269)	6 (271)	3 (274)	1 (276)	0 (277)
Int-2	48 (0)	21 (20)	12 (26)	4 (32)	2 (33)	0 (33)	0 (33)	0 (33)	0 (33)
AdvSM	259 (0)	63 (73)	18 (103)	5 (111)	1 (114)	0 (115)	0 (115)	0 (115)	0 (115)

	622 (0)	309 (309)	134 (479)	47 (564)	17 (594)	8 (603)	3 (607)	0 (610)	0 (610)
	271 (0)	124 (136)	55 (200)	25 (229)	9 (244)	6 (247)	3 (250)	1 (252)	0 (253)
	43 (0)	20 (20)	11 (26)	4 (33)	1 (35)	0 (36)	0 (36)	0 (36)	0 (36)
	273 (0)	54 (149)	15 (185)	4 (194)	1 (197)	0 (198)	0 (198)	0 (198)	0 (198)

C

Overall survival (%)

Time in study (years)

p<0·0001 (log-rank)

D

Progression-free survival (%)

Time in study (years)

p<0·0001 (log-rank)

Key for C and D
- AdvSM-1
- AdvSM-2
- AdvSM-3
- AdvSM-4
- Low
- Int-1
- Int-2

Number at risk (number censored)

AdvSM-1	35 (0)	16 (19)	3 (30)	2 (30)	0 (32)	0 (32)	0 (32)	0 (32)	0 (32)
AdvSM-2	38 (0)	12 (17)	3 (24)	0 (26)	0 (26)	0 (26)	0 (26)	0 (26)	0 (26)
AdvSM-3	117 (0)	22 (25)	5 (33)	1 (36)	0 (36)	0 (36)	0 (26)	0 (36)	0 (26)
AdvSM-4	39 (0)	3 (4)	0 (6)	0 (6)	0 (7)	0 (7)	0 (7)	0 (7)	0 (7)
Low	711 (0)	351 (356)	149 (556)	55 (650)	20 (685)	9 (696)	5 (700)	2 (702)	0 (703)
Int-1	299 (0)	144 (147)	63 (299)	30 (251)	9 (269)	6 (271)	3 (274)	1 (276)	0 (277)
Int-2	48 (0)	21 (20)	12 (26)	4 (32)	2 (33)	0 (33)	0 (33)	0 (33)	0 (33)

	32 (0)	14 (18)	3 (28)	2 (28)	0 (30)	0 (30)	0 (30)	0 (30)	0 (30)
	37 (0)	12 (19)	3 (28)	0 (31)	0 (31)	0 (31)	0 (31)	0 (31)	0 (31)
	106 (0)	18 (74)	4 (86)	1 (89)	0 (90)	0 (90)	0 (90)	0 (90)	0 (90)
	34 (0)	2 (25)	0 (27)	0 (27)	0 (27)	0 (27)	0 (27)	0 (27)	0 (27)
	622 (0)	309 (309)	134 (479)	47 (564)	17 (594)	8 (603)	3 (607)	0 (610)	0 (610)
	271 (0)	124 (136)	55 (200)	25 (229)	9 (244)	6 (247)	3 (250)	1 (252)	0 (253)
	43 (0)	20 (20)	11 (26)	4 (33)	1 (35)	0 (36)	0 (36)	0 (36)	0 (36)

Figure 3. Survival outcomes according to the IPSM score in patients with non-advanced and advanced systemic mastocytosis

Kaplan–Meier curves show the probability of overall survival (A, C) and progression-free survival (B, D) in patients with non-advanced and advanced systemic mastocytosis, defined by the IPSM.

Upper panels (A, B) show that patients with non-advanced systemic mastocytosis at low risk (no risk factors [low]) and intermediate risk (one [int-1] or two [int-2] additional risk factors) differed significantly and had a favourable outcome compared with patients with advanced systemic mastocytosis (AdvSM). Lower panels (C, D) show that patients with advanced systemic mastocytosis and no additional risk factors (AdvSM-1) differed significantly from those with one (AdvSM-2), two to three (AdvSM-3), or four to five (AdvSM-4) risk factors. IPSM=international prognostic scoring system for mastocytosis.

Table 1

Patients' characteristics and progressions recorded in the test and validation cohorts (pooled data)

	Childhood cutaneous mastocytosis	Adulthood cutaneous mastocytosis	Mastocytosis in the skin	Indolent systemic mastocytosis	Smouldering systemic mastocytosis	Aggressive systemic mastocytosis	Mast cell leukaemia	Mast cell sarcoma	Systemic mastocytosis with an associated haematological neoplasm	All patients
Test cohort										
Patients (n)	153	127	194	1006	53	62	23	2	174	1794
Age at diagnosis (years)	1 (0·15–16)	37 (18–76)	43 (18–87)	47 (17–83)	52 (25–79)	58 (17–83)	54 (27–90)	19 (8–30)	64 (22–83)	46 (0·15–90)
Female:male ratio	1:1·2	1:0·5	1:0·5	1:0·7	1:0·7	1:1	1:1·3	1:0	1:2·5	1:0·8
Tryptase (ng/mL)	6 (1–98)	9 (1–126)	12 (1–141)	31 (3–885)	200 (60–819)	175 (9–1432)	397 (114–4530)	3 (1–6)	150 (2–1022)	29 (1–4530)
Alkaline phosphatase (U/L)	212 (79–1729)	68 (33–212)	66 (36–290)	74 (22–317)	114 (36–345)	161 (63–1696)	194 (55–1121)	100 *201 (39–1407)	80 (22–1729)	
KIT Asp816Val positive	0/2 (0%)	23/98 (23%)	7/15 (47%)	680/799 (85%)	34/38 (89%)	38/45 (84%)	12/19 (63%)	0/2 (0%)	125/144 (87%)	919/1162 (79%)
Progression†	1/153 (1%)	5/127 (4%)	..	39/1006 (4%)	5/53 (9%)	11/62 (18%)	..	0/2 (0%)	27/174 (16%)	88/1577 (6%)
Progression to AdvSM†	0/153 (0%)	0/127 (0%)	..	27/1006 (3%)	5/53 (9%)	..	..	..	..	..
Validation cohort										
Patients (n)	0	18	0	384	11	19	5	0	25	462
Age at diagnosis (years)	..	33 (17–62)	..	46 (17–79)	52 (21–72)	61 (25–77)	65 (27–73)	..	61 (24–73)	47 (17–79)
Female:male ratio	..	1:0·2	..	1:0·9	1:1·8	1:1·4	1:1·5	..	1:3·2	1:1
Tryptase (ng/mL)	..	5 (2–19)	..	29 (6–664)	267 (161–380)	279 (72–2036)	196 (91–660)	..	82 (6–390)	31 (2–2036)
Alkaline phosphatase (U/L)	..	62 (44–125)	..	68 (17–332)	133 (49–553)	211 (68–1972)	82 (46–365)	..	124 (51–1310)	71 (17–1972)

	Childhood cutaneous mastocytosis	Adulthood cutaneous mastocytosis	Mastocytosis in the skin	Indolent systemic mastocytosis	Smouldering systemic mastocytosis	Aggressive systemic mastocytosis	Mast cell leukaemia	Mast cell sarcoma	Systemic mastocytosis with an associated haematological neoplasm	All patients
KIT Asp816Val positive	..	0/11 (0%)	..	333/356 (94%)	10/11 (91%)	17/18 (94%)	1/5 (20%)	..	18/24 (75%)	379/425 (89%)
Progression[†]	..	0/18 (0%)	..	6/384 (2%)	1/11 (9%)	3/62 (5%)	..	..	6/25 (24%)	15/462 (3%)
Progression to AdvSM[†]	..	0/18 (0%)	..	4/384 (1%)	1/11 (9%)	..	..	..	..	..

Data are median (range) or n/N (%), unless otherwise stated. AdvSM=advanced systemic mastocytosis.

*
Only one of the two patients had data for alkaline phosphatase available.

[†]
Disease progression was examined by analysing progression-related events defined by a shift from a known disease category in a higher graded (more advanced) form of mastocytosis or advanced haematological malignancy during follow-up.

Table 2

Effect of individual risk factors on overall survival and identification of prognostic variables

	Patients (n)	Risk population	Risk of patients with non-advanced mastocytosis				Risk of patients with advanced systemic mastocytosis			
			Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
			HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Male sex	1641	··	2·01 (1·14–3·55)	0·016	1·47 (0·67–3·14)	0·35	1·74 (1·20–2·54)	0·004	1·12 (0·67–1·86)	0·48
Age (years)	1641	60	1·11 (1·08–1·14)	<0·0001	10·75 (5·68–20·32)	<0·0001	1·04 (1·03–1·06)	<0·0001	2·14 (1·42–3·22)	<0·0001
Tryptase (ng/mL)	1530	125	3·01 (1·59–5·70)	<0·0001	1·61 (0·72–3·72)	0·24	1·66 (1·18–2·35)	0·0004	1·81 (1·20–2·75)	0·005
Leukocytes (× 10⁹ per L)	1543	16	2·08 (0·26–16·65)	0·491	··	··	1·94 (1·20–3·14)	0·007	1·88 (1·27–2·79)	0·002
Haemoglobin (g/dL)	1550	11·0	0·01 (0·00–0·31)	0·019	··	··	0·01 (0·00–0·04)	<0·0001	1·71 (1·13–2·57)	0·011
Platelets (× 10⁹ per L)	1543	100	0·05 (0·01–0·23)	<0·0001	5·78 (0·56–59·52)	0·14	0·17 (0·11–0·27)	<0·0001	1·63 (1·13–2·34)	0·009
Lactate dehydrogenase (U/L)	1226	260	0·46 (0·04–5·29)	0·535	··	··	2·51 (1·27–4·98)	0·008	1·36 (0·82–2·28)	0·19
Alkaline phosphatase (U/L)	1295	100	15·19 (3·93–58·71)	<0·0001	2·91 (1·60–5·30)	<0·0001	2·16 (1·35–3·46)	0·001	0·74 (0·39–1·40)	0·11
Calcium (mg/dL)	1216	8·7	0·01 (0·00–0·01)	0·003	0·97 (0·22–4·22)	0·93	0·01 (0·00–0·01)	<0·0001	1·48 (0·91–2·41)	0·12
Neutrophils (%)	1466	50	11·11 (0·72–171·57)	0·085	2·58 (0·90–7·44)	0·081	0·66 (0·30–1·46)	0·307	··	··
Monocytes (%)	1420	0·32	16·74 (0·19–1451·66)	0·216	··	··	3·20 (1·06–9·69)	0·040	1·43 (0·53–3·83)	0·44
Eosinophils granulocytes (%)	1432	··	1·01 (0·94–1·10)	0·749	··	··	1·00 (0·99–1·02)	0·408	··	··
Skin involvement	1641	··	1·06 (0·50–2·28)	0·877	··	··	0·44 (0·31–0·65)	<0·0001	0·46 (0·30–0·69)	<0·0001
Organomegaly *	1464	··	3·05 (1·56–5·94)	0·001	1·28 (0·56–2·94)	0·51	1·06 (0·68–1·66)	0·782	··	··
Mediator symptoms	1639	··	0·66 (0·36–1·20)	0·171	··	··	0·61 (0·43–0·85)	0·004	0·87 (0·52–1·48)	0·25
Allergy	1418	··	0·74 (0·39–1·43)	0·376	··	··	0·43 (0·22–0·84)	0·014	0·48 (0·20–1·19)	0·23

Prognostic variables were examined for their statistical power and independence from each other and from the WHO classification by univariate and multivariate analysis. HR=hazard ratio.

*
Organomegaly (ie, enlarged spleen, enlarged liver, enlarged lymph nodes, or a combination).