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Proposed International Prognostic Scoring System for Mastocytosis (IPSM)

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Abstract

***Background*:** The World Health Organization (WHO) classification separates mastocytosis into distinct entities, but a robust prognostication tool is not available.

***Methods*:** We analyzed the prognostic relevance of clinical and laboratory parameters in 1794 mastocytosis patients collected in the registry of the European Competence Network on Mastocytosis. For validation, 462 patients from the Spanish mastocytosis-network were examined.

***Results*:** The prognostic value of the WHO classification was confirmed ($p<0.005$). In non-advanced mastocytosis (n=1533), age ≥60 years and alkaline phosphatase ≥100 U/L were additional independent prognostic variables for survival, with a hazard ratio (HR) of 12.7 and 34.7, respectively. A new scoring system (IPSM) divided patients with non-advanced mastocytosis into three groups: low risk (no risk factors), intermediate-1 risk (one risk factor), and intermediate-2 risk (both risk factors). Overall survival (OS), progression-free survival (PFS), and event-free survival (EFS) differed significantly among these subgroups and between these subgroups and advanced systemic mastocytosis ($p<0.005$). In advanced mastocytosis (n=261), age ≥60 years (HR=2.3), tryptase ≥125 ng/ml (HR=1.6), leukocytes $\geq 16 \times 10^9$/L (HR=1.9), hemoglobin ≤11 g/dL (HR=1.9), platelets $\leq 100 \times 10^9$/L (HR=1.6) and skin involvement (HR=0.5) were prognostic variables. Based on these parameters, a separate score for advanced mastocytosis was established with significantly different outcomes concerning OS, PFS and EFS ($p<0.005$). The impact of both scores was confirmed in the Spanish validation-cohort.

***Conclusions*:** Using routinely applicable prognostic parameters, including age and alkaline phosphatase in non-advanced mastocytosis, and age, tryptase, blood counts and skin involvement in advanced disease, we have established a robust prognostication score ready for use in daily clinical practice.

Introduction

The diagnosis of mastocytosis is based on criteria provided by the World Health Organization (WHO) classification [1-4]. Most patients with cutaneous mastocytosis (CM), indolent systemic mastocytosis (ISM) and smoldering SM (SSM), have a stable clinical course and a normal or near normal life expectancy [5-15]. In contrast, patients suffering from advanced SM (AdvSM), including aggressive SM (ASM), SM with an associated hematologic neoplasm (SM-AHN) and mast cell leukemia (MCL) have a poor prognosis [5-15].

During the past two decades several clinical, serological, cytomorphological, immunological and molecular parameters have been reported to be of prognostic significance in mastocytosis [16,17-26]. Several of these variables have been included in the WHO classification [1-5]. Other adverse prognostic variables include absence of skin lesions, multi-lineage involvement with *KIT* D816V, mutations in genes other than *KIT*, including *SRSF2*, *ASXL1* or *RUNX1*, elevated serum ß2-microglobulin, and elevated alkaline phosphatase (AP) [16,17-26]. However, these parameters were studied in a limited number of patients and without comparing all potential parameters with each other in multivariate analyses. Moreover, several of these parameters, like molecular profiling, are not performed in all centers. Finally, the independent prognostic value of most variables has not been confirmed in larger patient cohorts to date.

In this study we used the data set of the registry of the European Competence Network on Mastocytosis (ECNM) to determine the prognostic impact of individual disease features and laboratory parameters in 1794 patients with mastocytosis. Based on the WHO classification and the prognostic factors identified, a scoring system ready for use in daily practice was established. This strength and impact of this international prognostic scoring system (IPSM) was confirmed in an independent validation-cohort.

Patients and Methods

Patients´ characteristics

Data from 2361 patients with mastocytosis seen between 1975 and 2017 in 24 centers in Europe and one US center (Stanford) were included in the ECNM registry (Table S3 in the Supplementary Appendix) [27]. Various clinical and laboratory parameters were captured at diagnosis and during follow up (Table S4 A-D in the Supplement). Follow up data were recorded in 1794 patients (median age: 46 years; range: 0.15-90), including 1006 (56.1%) ISM, 269 (15.0%) CM, 174 (9.7%) SM-AHN, 62 (3.5%) ASM, 53 (3.0%) SSM, 23 (1.3%) MCL, and 2 mast cell sarcoma (MCS, 0.1%) patients (Figure S1, Table S5 and S6 in the Supplementary Appendix). In 205 adult patients (11.4%) typical mast cell infiltrates in the skin were found, but no bone marrow (BM) examination was performed. These patients were included as mastocytosis in the skin (MIS) and were integrated in the non-advanced SM category for prognostication regarding survival [28]. The median observation-time was 3.4 years (range: 0.01-36) (Figure S2 in the Supplement). The validation cohort consisted of 462 patients (384 ISM, 25 SM-AHN, 19 ASM, 18 CM, 11 SSM, and 5 MCL) collected in the Red Española de Mastocitosis (REMA; Table S7 in the Supplement).

Statistical analyses

Overall survival (OS; time from diagnosis to death), progression-free survival (PFS; time from diagnosis to progression) and event-free survival (EFS; time from diagnosis to progression or death) were analyzed according to the method of Kaplan and Meier with Mantel-Cox tests for group comparisons. Since MCL is an end-stage disease (no further progression can occur) and MIS is a provisional diagnosis for patients with skin-involvement but unknown/unavailable bone marrow, these two patient-groups were excluded from PFS analysis. A description of

statistical analyses, including univariate (likelihood ratio and Kruskal Wallis test) and multivariate analyses is provided in the Supplement.

Development of IPSM for non-advanced and advanced mastocytosis

Based on results obtained in multivariate analyses, we developed two prognostic scoring systems, one for patients with non-advanced mastocytosis (non-AdvM i.e. CM, MIS, ISM, SSM) and one for AdvSM where organ damage leads to reduced survival [5,6]. Details about the development of the score and its validation are described in the Supplement.

Results

Prognostic impact of the WHO classification

The WHO classification´s prognostic significance concerning OS and PFS was confirmed in the total cohort of patients ($p<0.005$) (Figure 1). Our registry data also confirmed that the WHO classification defines two prognostic groups: patients with non-advanced mastocytosis and those with AdvSM. However, even among cases with non-AdvM, subtle but significant differences could be substantiated in this large data set. Likewise, patients with CM had superior OS compared to all other subgroups, including ISM (Figure 1A). There was no substantial difference in OS when comparing childhood CM (aged<18 years; n=142) and adulthood CM (age ≥18 years, n=127; Figure S2 in the Supplement). Survival at 10 years and median OS in ISM were 93.5% and 28.4 years, respectively. In CM, MIS and SSM, the 10 year survival was 100%, 93.0% and 84.5%, respectively. The median OS was not reached in these entities. In ASM, MCL, SM-AHN, MCS and SM-AHN, median OS was 5.7, 1.9, 1.1, and 2.9 years, respectively (Figure 1A).

The median EFS of all patients was 25.5 years (Figure S3 in the Supplement). Overall, 239 events were recorded. As expected, CM patients had the best outcome with only 6 events (2.2%). More events were documented in cases with MIS (n=10; 5.0%), ISM (n=62; 6.2%), SSM (n=7; 13.2%) and AdvSM (n=154; 59.0%). In patients with ASM, MCL, MCS, and SM-AHN, the median EFS was 5.0, 1.9, 1.1, and 2.7 years, respectively ($p<0.005$; Figure S4 in the Supplement).

After exclusion of MIS and MCL cases, PFS was analyzed in 1566 patients. Progression of disease was observed in 88/1566 patients (5.6%), including 39/1006 patients with ISM (3.9%), 5/53 SSM patients (9.4%), 11/62 ASM cases (17.7%) and 27/174 patients with SM-AHN (15.5%) (Table 1). In CM, 6/269 cases developed ISM. Overall, PFS at 10 years was 88.0%

(Figure 1B). Differences in PFS between the WHO cohorts were significant (p<0.005). None of the WHO groups reached the median PFS (Figure 1B).

Proposed IPSM for Non-Advanced Mastocytosis

Various laboratory and clinical variables, including age, blood counts, serum tryptase levels, lactate dehydrogenase (LDH), AP, WHO classification, organomegaly, mediator-related symptoms, and known allergies were analyzed by uni- and multivariate analyses. In patients with non-AdvM, age ≥60 years and AP ≥100 units/liter were identified as significant independent predictors of evolution to ´higher grade mastocytosis´ (hazard ratio=HR: 4.0 and 2.5, respectively) and of OS (HR: 12.7 and 34.7, respectively) (Table 2). In patients with non-AdvM, an AP ≥100 units/liter was also associated with a significantly higher rate of progression to a higher-grade SM (AdvSM) (Supplementary Table 8). Based on these variables, we established a simple prognostic scoring system (IPSM) and applied it in 1085 patients with non-AdvM where all variables were available. Patients with non-AdvM without additional risk-factors comprised the low-risk group (low), and those with one or two risk factors the intermediate-risk group 1 (int-1) and intermediate risk-group 2 (int-2), respectively. Patients with AdvSM (n=261) had the worst outcome.

OS at 10 years was 98.1% in the low risk group, 87.1% in the int-1 group, 52.1% in the int-2-risk group, and 22.0% in the AdvSM group (p<0.005) (Figures 2A). Significant differences were also observed in the rate of progression, with a PFS at 10 years of 96.3% in low risk patients, 87.1% in int-1 patients, 76.3% in int-2 patients, and 60.8% in the AdvSM group (Figure 2B). The significance of the score was also confirmed for OS in MIS and ISM and for PFS in CM, ISM, and SSM (p<0.005) (Figure S6 and S7 in the Supplementary Appendix). In SSM, the differences in OS were not significant (p=0.09) which may be due to the relatively low number of patients. The score was also of prognostic significance regarding EFS in all subgroups (p<0.05) (Figure S8-S9 in the Supplementary Appendix).

Proposed IPSM for Advanced Mastocytosis

In patients with AdvSM, age ≥60 years (HR=2.3), tryptase ≥125ng/ml (HR=1.6), leukocytes ≥16x10^9/L (HR=1.9), hemoglobin ≤11g/dL (HR=1.9) platelets ≤100x10^9/L (HR=1.6), and skin-involvement (HR=0.5) were independent prognostic variables concerning OS in multivariate analyses (Table 2). These parameters were employed to optimize scoring in AdvSM. Each risk factor with a HR >1.5 scored 1 point, and skin-involvement (HR 0.5) scored -1 point. By adding all risk points, 4 different risk groups were established. The score was applied in 231 patients with AdvSM where all variables were available. Significant differences were observed among the cohorts with AdvSM-1 (-1 to 0 points), AdvSM-2 (1 point), AdvSM-3 (2 to 3 points), and AdvSM-4 (4-5 points; $p<0.0005$) (Figure 2C and D). The calculated OS of patients with AdvSM-1 was between the OS of int-1 and the OS of the int-2 risk group of patients with non-advanced disease (Figure 2C). The significance of the score for AdvSM was also confirmed for PFS and EFS, and for individual WHO entities: ASM, MCL and SM-AHN ($p<0.005$) (Figure 2D, Figure S10-13 and Table S9 in the Supplement).

Validation of the IPSM in an Independent Sample-Cohort

The IPSM was validated using a patient cohort provided by the Spanish mastocytosis network, REMA. Validation was performed for patients with non-AdvM and patients with AdvSM. Both scores showed significant results in the validation sample (non-AdvM: n=413, $p<0.005$; AdvSM: n=49, $p<0.005$), confirming the prognostic power and usefulness of the IPSM (Figure S14 in the Supplement).

Discussion

Although the WHO classification is a well-established diagnostic approach with prognostic impact, an advanced tool of prognostication for mastocytosis is lacking. Notably, prognosis and survival of patients within distinct WHO subgroups vary substantially [15,16,28]. We employed the largest cohort of patients ever collected, the ECNM registry data-set, with the aim to define new prognostic variables and to improve prognostication. Using this data set, we identified independent prognostic variables for patients with non-AdvM (age and AP) and AdvSM (tryptase, blood counts, absence of skin-involvement). Based on these parameters, we established a simple prognostic score system, the IPSM. The predictive value of this new score was confirmed in an independent validation cohort provided by the REMA.

So far it remained unknown whether adult patients with CM have a favorable outcome compared to ISM. In our study, adult patients with CM were found to have the same excellent OS that was also recorded in childhood CM and that is clearly superior to the OS in ISM or MIS. We also found that patients with MIS and ISM have a similar OS, suggesting that most patients with MIS may indeed suffer from ISM. This observation supports the recommendation that a BM study should be performed in all adult patients with MIS. So far, it remains unknown why adult patients with CM have a better OS compared to ISM or MIS. One explanation would be that ISM is a more advanced disease with higher risk of progression to AdvSM. An alternative explanation could be the higher median age of SM patients (MIS: 41 years; ISM: 47 years) compared to adult CM patients (36 years).

Several clinical and laboratory parameters are known to serve as prognostic variables in mastocytosis [8-10,13,16-26]. In patients with non-advanced SM, AP ≥100 U/L and age ≥60 years were the two major independent predictors of survival and were therefore employed to establish a simple score-system. AP has already been shown to be of prognostic value in SM in previous studies [16,17,29]. Moreover, an elevation in AP levels may reflect SM-mediated

organ damage in the bones and/or the liver [30-32]. High AP levels found in some patients with non-AdvM may thus indicate a clinically silent organ involvement. Such occult liver involvement may produce an elevated AP even before the disease progresses to AdvSM. Indeed, we found a significantly higher rate of progression from ISM/SSM to AdvSM in patients with AP ≥100 units/liter.

Analyzing the median age in our patients, we found that age increases constantly from low (43 years) to int-1 (53 years) and int-2 (64 years) patients. A simple explanation for this observation would be that reduced life expectancy is primarily due to the higher age in these patients. However, not only OS, but also PFS differed significantly among these patients. Thus, our results cannot only be explained by differences in the ´natural´ age-dependent life expectancy. With regard to PFS, it is tempting to speculate that an increased clonal instability at higher age might contribute to a higher rate of progression. Indeed, it is known that the number of mutations in hematopoietic (stem) cells increases with age [33,34].

Recently, organomegaly was found to be of prognostic significance in SM [17,29]. In the present study, organomegaly defined by enlarged spleen and/or liver and/or lymphadenopathy was not an independent prognostic factor for OS which may be explained by the fact that organomegaly is represented in the WHO criteria as either B-finding (without organ dysfunction) or as C-finding (with organ damage) [3-4].

A number of previous studies have shown that patients with AdvSM often lack skin involvement [3-5]. In the present study, the absence of typical skin lesions was of prognostic significance in multivariate analysis in AdvSM, but not in patients with non-AdvM. This result has several explanations. First, it is well known that skin lesions are preferentially absent in patients with rapidly progressive ASM and MCL. Second, there is also a subgroup of ISM patients in whom no skin lesions are found and the clinical course remains stable. Contrasting AdvSM, these patients have a low mast cell burden and a favorable prognosis, and are now-a-days classified as isolated BM mastocytosis [2-5].

In AdvSM prognostication is of utmost clinical importance. Thus, we analyzed the prognostic impact of potential prognostic factors in this group separately. Again, age turned out to be of prognostic importance. Other prognostic parameters were elevated tryptase, abnormal blood counts, and absence of skin-involvement. Using these variables, high-risk AdvSM patients were split into four groups, AdvSM-1, AdvSM-2, AdvSM-3, and AdvSM-4, with significant differences regarding OS, EFS and PFS. An interesting observation was that the prognosis of int-1 risk and int-2 risk patients overlaps with that found in patients with AdvSM-1. This observation supports the strengths and impact of the IPSM. Thus the IPSM may identify patients with a higher risk than expected by the WHO classification.

The importance of prognostic variables in SM has been discussed in previous studies. Likewise, an elevated ß2-microglobulin, multi-lineage involvement of leukocytes with *KIT* D816V, the *KIT* D816V allele burden, and mutations in additional genes were reported to be of prognostic significance in SM [6,16,17,35]. In the current study, molecular markers were only available in a small subset of patients collected in the ECNM registry which shows that their use is still restricted to relatively few specialized centers. Moreover, molecular abnormalities are preferentially detected in patients who have advanced SM, such as SM-AHN. In the IPSM we included prognostic parameters that are of major (and independent) prognostic impact and are easily accessible in daily practice. In this regard it should be emphasized that in patients with non-AdvM, our score is based on only two basic risk-factors (age and AP), but is robust in that the physician can readily detect patients who have a poor prognosis, similar to the risk and outcome in patients with AdvSM. These non-AdvM patients need to be monitored closely (as patients with AdvSM) to detect progression and to define the optimal time of intervention.

In the light of novel therapeutic options, our score may also support treatment decisions in SM. Patients with AdvSM usually require cytoreductive therapy and the optimal way of treatment depends on patient-related factors, disease aggressiveness, and the presence of an AHN [5,36,37]. At present therapeutic options for slowly progressing AdvSM include (off-label)

interferon-alpha, cladribine, and midostaurin which was approved for use in AdvSM in 2017 [5,36-39]. By contrast, in AdvSM with rapid progression or MCL, poly-chemotherapy is often considered, and if possible, hematopoietic stem cell transplantation (HSCT) is performed [32-37]. However, the curative potential of this therapy has to be weighed against side effects [5,36-40]. For example, in older patients with slowly progressing AdvSM with low risk IPSM, therapy with midostaurin or cladribine may be a reasonable option [5,36].

In summary, the WHO classification remains an important basic prognostication tool in mastocytosis. However, age and AP in non-advanced SM, and age, tryptase, blood counts and skin involvement in AdvSM, are also of prognostic significance. By applying the related new score, the IPSM, prognostication in mastocytosis may improve substantially and should thus support care-providers in daily clinical practice and study teams in clinical trials.

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Legends to Figures

Figure 1

Survival probability in different WHO subgroups of mastocytosis

The probability of overall survival, OS (A) and progression-free survival, PFS (B) in subgroups of mastocytosis defined by WHO criteria was calculated according the method of Kaplan and Meier. Mast cell leukemia (MCL), the most aggressive mast cell disorder where progression to a higher disease state is not possible and mastocytosis in the skin (MIS), a provisional diagnosis in patients with proven skin involvement but unknown/unavailable bone marrow, were excluded from PFS analysis. Differences in OS and PFS between the WHO groups were statistically significant as assessed by log rank test ($p<0.005$). As visible, patients with non-advanced mastocytosis i.e. cutaneous mastocytosis (CM), MIS, indolent systemic mastocytosis (ISM) and smoldering SM (SSM) have a much better prognosis compared to patients with advanced SM, namely aggressive SM (ASM), MCL, mast cell sarcoma (MCS) and SM with an associated hematologic neoplasia (SM-AHN). OS and PSF in individual AHN subgroups of SM-AHN are shown in Supplementary Figures 5.

Figure 2

Overall survival (OS) and progression-free survival (PFS) of patients with mastocytosis according to the international prognostic scoring system for mastocytosis (IPSM)

OS was determined in all patients in whom the score could be calculated. Mast cell leukemia, the most aggressive mast cell disorder (cannot progress into a more aggressive variant) and mastocytosis in the skin (MIS), a provisional diagnosis for patients with proven skin involvement but unknown/unavailable bone marrow results, were excluded from analysis of PFS. A, B: OS (A) and PFS (B) were estimated according to the method of Kaplan and Meier. In these analyses, patients with Low, Intermediate (Int)-1, and Int-2 risk groups differed

significantly in their OS and PFS and had a favourable outcome compared to patients with advanced systemic mastocytosis (AdvSM) according to log rank test ($p<0.005$). C, D: Estimated OS (C) and PFS (D) according to the IPSM for patients with AdvSM. OS and PFS differed significantly between the cohort without risk factors (AdvSM-1), patients with one risk factor (AdvSM-2), those with two to three risk factors (AdvSM-3), and those with four to five risk factors (AdvSM-4) ($p<0.0005$). The OS of patients in the risk groups AdvSM-1 and AdvSM-2 were similar to that of non-advanced mastocytosis patients in the Int-1 and Int-2 risk group, respectively.

Table 1
Evolution patterns and numbers of progression events in patients with mastocytosis

Diagnosis	Progression		Number of patients in subgroups	Median time to progression (years)	Number of patients n (%)
	from	to			
CM	MPCM	ISM	6	5.2	6 (6.8)
ISM	ISM	SSM	12	5.5	39 (44.3)
	ISM	ASM	9	3.0	
	ISM	MCS	1	7.9	
	ISM	SM-AHN[1]	17	1.9	
SSM	SSM	ASM	4	4.6	5 (5.7)
	SSM	SM-AHN[2]	1	0.7	
ASM	ASM	MCL	5	1.8	11 (12.5)
	ASM	SM-AHN[3]	6	1.3	
SM-AHN	ISM-AHN	ASM-AHN	3	2.3	27 (30.7)
	ASM-AHN	MCL-AHN	7	1.2	
	ASM-CMML	MCL-AML	1	2.8	
	SM-CEL[4]	SM-AML	1	1.0	
	SM-MPN[5]	SM-AML	4	2.4	
	SM-CMML[6]	SM-AML	4	2.2	
	SM-MDS/MPN[7]	SM-AML	2	1.6	
	SM-MDS[8]	SM-AML	5	1.0	
All patients				2.2	88 (100)

Disease evolution was examined by analyzing progression-related events defined by a shift from a known disease category in a higher-graded (more advanced) form of mastocytosis or AHN during follow up. Abbreviations: AML, acute myeloid leukemia, ASM, aggressive systemic mastocytosis; CEL, chronic eosinophilic leukemia; CM, cutaneous mastocytosis; CMML, chronic myelomonocytic leukemia, ISM, indolent systemic mastocytosis; MCL, mast cell leukemia; MCS, mast cell sarcoma; MDS, myelodysplastic syndrome; MPN, myeloproliverative neoplasm; MDS/MPN, myelodysplastic/myeloproliferative overlap syndrome; n, number; SM-AHN, systemic mastocytosis with an associated hematologic neoplasm; SSM, smoldering systemic mastocytosis.

[1] i.e. ASM-CMML, n=3; ISM-NHL, n=3; ISM-AML, n=2; ISM-CML, n=2; ISM-MPN, n=2; ISM-CMML, n=1; ISM-other, n=1; SSM-CMML, n=1; SSM-other, n=2

[2] i.e. SSM-CMML

[3] i.e. ASM-AML, n=3; AML-CMML, n=2; ASM-MDS/MPN, n=1

[4] i.e. ASM-CEL, n=1

[5] i.e. ASM-MPN, n=3; MCL-MPN, n=1

[6] i.e. ASM-CMML, n=2; ISM-CMML, n=2

[7] i.e. ASM-MDS/MPN, n=2

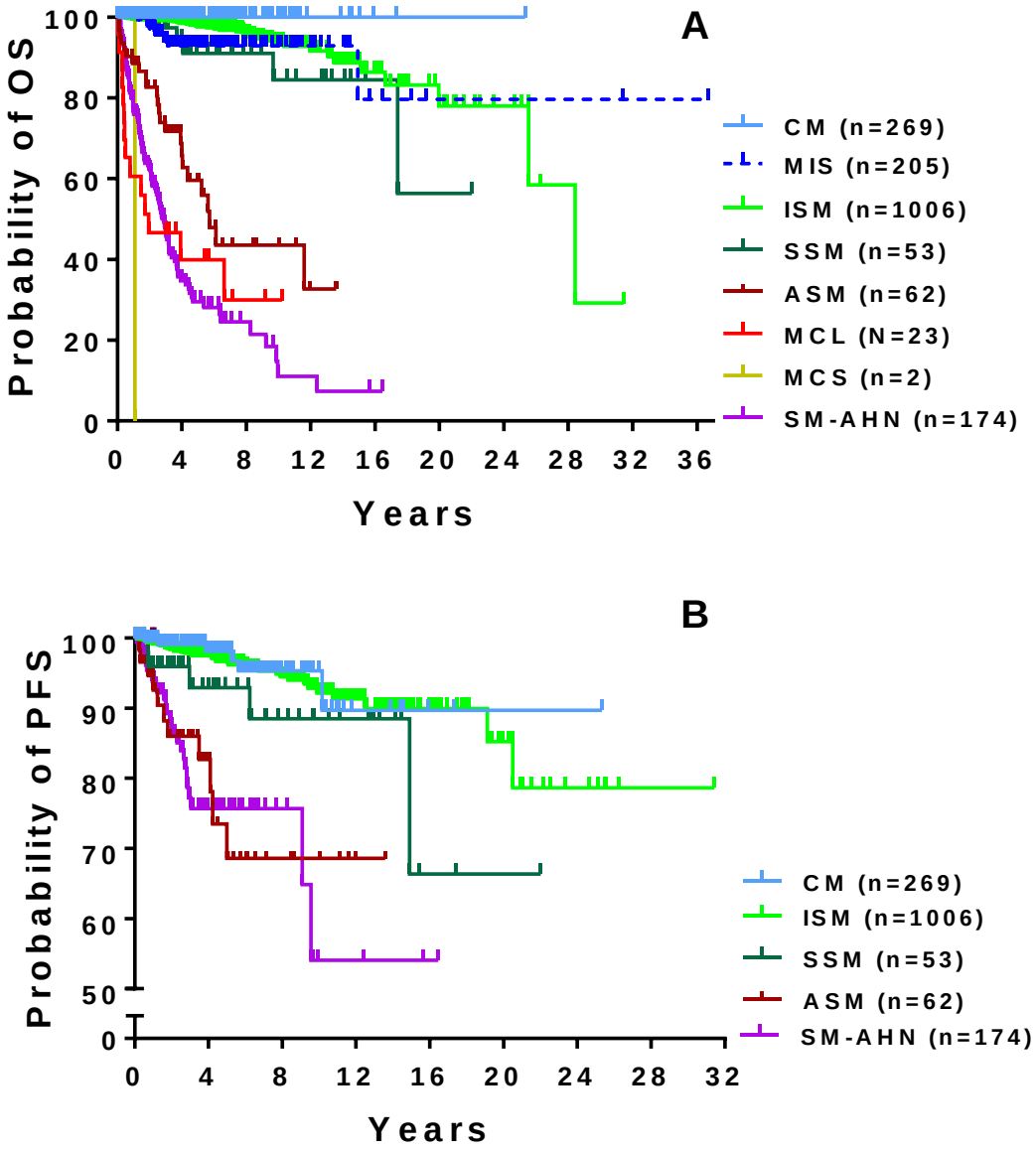
[8] i.e. ASM-MDS, n=2; ISM-MDS n=3

Table 2

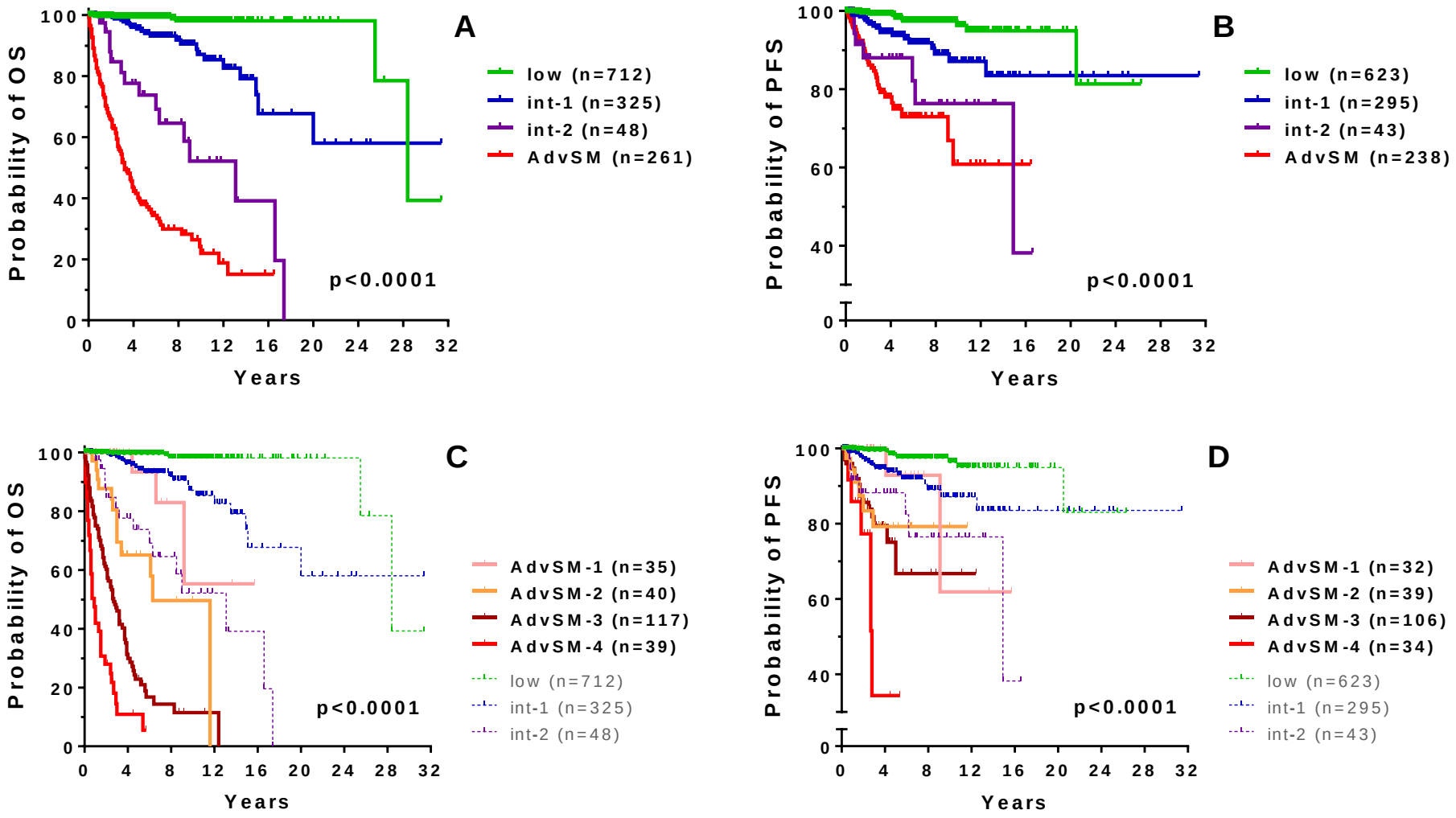
Impact of the risk-factors on survival and identification of independent prognostic variables in multivariate analyses

Variable	Number of patients n	Risk popu-lation	Non-advanced systemic mastocytosis						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	1794	-	1.80	1.02-3.15	0.041			n.s.	1.76	1.21-2.55	0.003			n.s.
Age (years)	1794	≥60	1.11	1.08-1.14	<0.001	12.66	6.10-26.29	<0.001	1.04	1.02-1.05	<0.001	2.05	1.37-3.06	<0.001
Tryptase (ng/mL)	1625	≥125	3.27	1.76-6.06	<0.001			n.s.	1.66	1.19-2.32	0.003	1.91	1.26-2.89	0.030
Leukocytes ($x10^9$/L)	1609	≥16	2.23	0.28-17.50	0.445			-	1.83	1.14-2.93	0.012	1.88	1.26-2.77	<0.001
Hb (g/dL)	1618	<11.0	0.01	0.00-1.03	0.051			-	0.01	0.00-0.03	<0.001	1.71	1.12-2.60	<0.001
PLT ($x10^9$/L)	1608	<100	0.05	0.01-0.20	<0.001			n.s.	0.17	0.11-0.26	<0.001	1.62	1.26-2.34	0.010
LDH (U/L)	1250	≥250	0.47	0.04-5.15	0.535			-	2.67	1.36-5.25	0.007			n.s.
AP (U/L)	1332	≥100	8.48	2.58-27.85	<0.001	34.71	3.93-306.50	<0.001	2.32	1.45-3.70	<0.001			n.s.
Ca (mg/dL)	1241	≤8.9	0.01	0.00-0.01	<0.001			n.s.	0.01	0.00-0.01	<0.001			n.s.
Neutrophils (%)	1528	≥50	14.69	1.08-198.77	0.043			n.s.	0.65	0.29-1.43	0.281			-
Monocytes (%)	1493	≥8.7	12.16	0.14-1035.14	0.271			-	3.35	1.10-10.19	0.033			n.s.
Eosinophils (%)	1493	-	0.56	0.01-31.74	0.777			-	1.03	0.45-2.36	0.936			-
Skin involvement	1794	-	0.95	0.44-2.04	0.895			-	0.46	0.32-0.67	<0.001	0.45	0.30-0.67	<0.001
Organomegaly*	1655	-	3.09	1.60-5.98	<0.001			n.s.	1.15	0.76-1.72	0.513			n.s.
Mediator symptoms	1792	-	0.77	0.42-1.40	0.389			-	0.58	0.41-0.82	0.002			n.s.
Allergy (y/n)	1502	-	0.78	0.41-1.50	0.454			-	0.41	0.21-0.81	0.010			n.s.

Prognostic variables were examined for their statistical power and independence from each other and from the WHO classification by uni- and multivariate analysis. AP, alkaline phosphatase; Ca, calcium; CI, confidence interval; CM, cutaneous mastocytosis; Eosinophils, eosinophil granulocytes; Hb, hemoglobin; HR, hazard ratio; LDH, lactate dehydrogenases; n.s., not significant and excluded in stepwise Cox regression; PLT, platelets; *Organomegaly i.e. enlarged spleen and/or enlarged liver and/or enlarged lymph nodes



Sperr et al., Fig. 1



Sperr et al., Fig. 2