Importance of adequate diagnostic work-up for correct diagnosis of advanced systemic mastocytosis

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Abstract

Background:

Little is known about epidemiology of advanced systemic mastocytosis (advSM).

Objectives:

We sought to investigate epidemiologic features and diagnostic pitfalls of advSM in Germany.

Methods:

Therefore, 140 patients from a single German reference center of the European Competence Network on Mastocytosis between 2003 and 2018 were analyzed.

Results:

Median age was 68 years (range 26-86), male vs. female ratio was 2:1. An elevated serum tryptase, a *KIT* D816 mutation and additional somatic mutations, e.g. in *SRSF2*, *ASXL1* or *RUNX1* (*S*/*A*/*R*), were identified in 95%, 91% and 74% of patients, respectively. Median overall survival was 3.5 years (range 0.03-14.3; male vs. female 2.6 vs. 4.2 years, p=0.02). Two categories of misdiagnoses were identified in 51/140 (36%) patients: Firstly, systemic mastocytosis (SM) was overlooked in 28/140 (20%) patients primarily diagnosed with various subtypes of myeloid neoplasms. Secondly, 23/140 (16%) patients were diagnosed with supposed progression from indolent SM (ISM) to advSM; however, combination of an elevated *KIT* D816V variant allele frequency (VAF) in peripheral blood (n=22), monocytosis (n=9), eosinophilia (n=6) and/or mutations in *S*/*A*/*R* (n=10) suggest that distinct signs of potential advSM were overlooked in virtually all patients. Based on locally diagnosed patients in an area of 2.5 million inhabitants, but obviously without considering more, yet unrecognized cases, incidence and prevalence of advSM is at least 0.8 and 5.2, respectively, per 1 million inhabitants.

Conclusions: Adequate analyses of tryptase levels, bone marrow morphology and genetics in patients with myeloid neoplasms or SM would help to prevent the significant underdiagnosis of advSM.

Key words

Epidemiology, incidence and prevalence of advSM, misdiagnosis, multilineage involvement, disease awareness

Abbreviations

AAR: Aachen City Region
advSM: advanced systemic mastocytosis
AML: acute myeloid leukemia
BM: bone marrow
CEL: chronic eosinophilic leukemia
CLL: chronic lymphocytic leukemia
CMML: chronic myelomonocytic leukemia
EAB: expressed allele burden
ECNM: European Competence Network on Mastocytosis
HES: hypereosinophilic syndrome
ISM: indolent systemic mastocytosis
MARS: mutation adjusted risk score
MC: mast cell
MCL: mast cell leukemia
MPN: myeloproliferative neoplasm
MDS/MPN: myelodysplastic/ myeloproliferative neoplasm
MPRN: Metropolitan Region Rhein-Neckar
NGS: next generation sequencing
OS: overall survival
RNA: ribonucleid acid
SM: systemic mastocytosis
SM-AHN: systemic mastocytosis with associated hematologic neoplasm
SSM: smoldering systemic mastocytosis
VAF: variant allele frequency
WHO: world health organization

Highlight Box:

- **Little is known about epidemiology of advanced systemic mastocytosis (advSM) given the heterogenic nature of the disease.**
- **We describe epidemiologic aspects and potential pitfalls in the diagnostic work-up of advSM in Germany contributing to a better understanding and increased awareness of the disease.**

- **Potential signs of AdvSM should be taken into consideration more frequently in the diagnostic work-up of suspected indolent systemic mastocytosis. Testing for serum tryptase levels and *KIT* D816V should be implemented in the routine work-up of mastocytosis.**

Introduction

Systemic mastocytosis (SM) is a rare myeloid neoplasm characterized by abnormal mast cell (MC) proliferation and accumulation in various organs such as bone marrow (BM), visceral organs and skin [1, 2]. The current WHO classification recognizes SM as a separate myeloid neoplasm [2, 3, 4]. Mutations in the KIT gene, usually *KIT* D816V, are a pathogenetic and diagnostic hallmark that is present in >90% of patients with SM [2, 5, 6]. Depending on type and degree of organ infiltration and subsequent organ damage, SM is classified into "non-advanced" subtypes, e.g. indolent SM (ISM) and smoldering SM (SSM), and into advanced SM (advSM) which comprises SM with an associated hematologic neoplasm (SM-AHN), aggressive SM (ASM), and mast cell leukemia (MCL)[1, 7].

While life expectancy is not significantly impacted in patients with ISM [8, 9], advSM is associated with a poor prognosis with a median survival ranging between 6 and 18 months in MCL and between 2 and 4 years in SM-AHN and ASM [10, 11]. The poor prognosis of patients with advSM is closely related to the presence and number of additional somatic mutations, e.g. in *SRSF2*, *ASXL1* or *RUNX1* (*S/A/R* gene panel)[12-14]. Most of the recently reported prognostic scoring systems include a combination of clinical characteristics and additional somatic mutations[14-16].

To date, relatively little is known about the incidence and prevalence of SM and its subtypes. A Danish analysis reported an overall incidence of SM (including over 80% of patients with ISM) of 0.9 per 100,000 per year [17]. Van Doormaal et al. reported a prevalence of ISM of 13 per 100,000 inhabitants in the Netherlands [18]. However, since initial reporting, the incidence and prevalence may have risen due to

improved disease awareness and more widely available diagnostic tests, particularly serum tryptase and mutation analysis. The European Competence Network on Mastocytosis (ECNM) is focusing on the improvement of diagnosis and treatment of SM and comprises reference centers and centers of excellence all over Europe[19, 20]. Between 2009 and 2018, 140 patients with advSM were referred to our ECNM center from all over Germany. On basis of both our local and the overall patient cohort from Germany and through comparison with data from a second and independent ECNM center, we sought to analyze epidemiologic characteristics of advSM.

Methods

We retrospectively evaluated 140 patients with advSM who were referred, diagnosed and treated at our ECNM center for mast cell disorders between January 2009 and December 2018. Classification of patients was based on established WHO criteria [3]. All patients gave written informed consent and were registered in the 'German Registry on Disorders of Eosinophils and Mast Cells'. The study design adhered to the tenets of the Declaration of Helsinki and was approved by the institutional review board of the Medical Faculty of Mannheim, University of Heidelberg.

Mutation analysis for *KIT* D816V on RNA level and NGS analysis for additional mutations was performed as previously described[6, 12].

Statistical analyses were performed using GraphPad prism 8 software, San Diego, California or SAS, release 9.4 (SAS Institute Inc., Cary, North Carolina, USA). For qualitative factors absolute and relative frequencies are given. Quantitative variables are presented by median values together with corresponding ranges. Survival probabilities were calculated by the Kaplan-Meier Method, correlation between variables was

investigated using Mann-Whitney-U-test (t-approximation). In general, a test result with p less than 0.05 has been considered as statistically significant.

Results

Sex/Age. There was a significant male predominance (2:1; male, n=94; female, m=46). Median age at diagnosis of advSM was 68 years (range, 26-86; female vs. male, median 67.2 vs. 69.5 years, p=0.024). Median distance from hometown to our referral center was 194 (range 2-723) km. Distance was <50 km in 29 (21%) patients, 50-100 km in 15 (11%), 100–200 km in 30 (21%) and >200 km in 66 (47%) of patients. Therefore, more than half of the patients came to our center from beyond the close vicinity (Figure 1, Supplementary Figure 1). Patient characteristics are listed in Table 1.

Mutations. A mutation in *KIT* was detectable in 136/140 (97%) patients, predominantly *KIT* D816V (132/140, 94%). In 96% of *KIT* D816V positive patients, the mutation could be detected in BM and peripheral blood (PB), only 5 patients who were tested positive in BM were negative in PB using RNA-based quantitative real time PCR technique [6]. The median *KIT* D816V expressed allele burden (EAB, i.e. quantification of the *KIT* D816V allele burden on RNA level) in PB was 29% (range 0-77%). Two patients (1%) were positive for *KIT* D816H and *KIT* D816Y, respectively. At time of progression from ISM to advSM, a *KIT* mutation was detectable in PB of 22/23 (96%) patients (*KIT* D816V, n=21; *KIT* D816H, n=1). Targeted next-generation sequencing (NGS) was performed in 130/140 patients. At least one additional mutation was found in 103/130 (79%) patients, with a statistically significant misbalance between male and female (male, 76/87, 87% vs. female, 27/43, 63%, p=0.0057) patients. In 57/76 (75%) male patients and 17/27 (63%) female patients, at least one mutation in the *S/A/R* gene panel was identified.

Classification of SM. The 140 patients were sub-classified as SM-AHN (n=105, 75%), ASM (n=9, 6%) and MCL (n=26, 19%). Interestingly, 17/26 patients with MCL presented with MCL-AHN. AHN overall comprised chronic myelomonocytic leukemia (CMML, 44/122, 36%), myelodysplastic/myeloproliferative neoplasm (MDS/MPN unclassifiable, 31/122, 25%), MDS (13/122, 11%), hypereosinophilic syndrome/chronic eosinophilic leukemia, not otherwise specified (HES/CEL-NOS, 12/122, 10%), various subtypes of MPN (12/122, 10%), acute myeloid leukemia (AML, 15/122, 12%), chronic lymphocytic leukemia (CLL) or lymphoma (3/122, 2%) and multiple myeloma (1/122, 1%).

***De novo* advSM vs. advSM with history of ISM.** The majority of patients was diagnosed with *de novo* advSM (n=117, 84%) without a history of ISM. In 29 patients (21%), BM analysis at initial presentation revealed various hematologic disorders including CMML (n=6), MDS (n=5), MPN (n=5), MDS/MPN (n=4), immune thrombocytopenia (n=4), lymphoma (n=2), reactive conditions (n=2), HES (n=1) and one patient with metastatic breast cancer (n=1) but failed to identify an underlying SM. Only a repeated investigation led to correct diagnoses median 24 months (range 1.3-86) after initial diagnosis.

In a cohort of 23 patients, the diagnosis of advSM was established median 32 months (range 1-165) after initial diagnosis of ISM ("advSM with history of ISM"). All those patients presented with features of a multilineage and/or multimutated myeloid disease process, with measurable *KIT* D816V EAB in PB (22/23, 96%), somatic mutations (14/22, 64%) in the *S*/*A*/*R* gene panel (10/22, 46%) or other genes (n=4; *JAK2*, n=3; *TET2*, n=3; *CBL*, n=1; *EZH2*, n=1) and/or alternative features of myeloid proliferation, e.g. monocytosis or eosinophilia (13/23, 57%). In the absence of morphologically proven AHN or C-findings, these features are in clear favor of an ISM with multilineage involvement or an overlooked SM-AHN. The majority of patients therefore presented with SM-AHN or MCL-AHN (17/23, 74%). Interestingly, C-findings were only

present in 8/23 (35%) patients in this cohort which may be due to the fact that the SM component in SM-AHN was often ISM and some of the cases with MCL had chronic MCL without C-findings.

Incidence and prevalence. In the last 15 years, the median number of newly referred patients was 10 per year (range 0-19, Figure 1) and the median number of patients being managed at our site was 34 (range 1-74) per year, with higher numbers following the initiation of the midostaurin trial [21] in 2009 (median number of new referrals, n=13, range 5-19; ongoing patients, n=57, range 21-74; Figure 2a/b).

Because of the significant heterogeneity of referrals from various regions of Germany (map), we subsequently focused for calculation of incidence and prevalence of advSM in Germany on patients from the closer environment of the University Hospital Mannheim, the so-called Metropolitan Region Rhein-Neckar (MPRN, Supplementary Figure 1) with 2.4 million inhabitants. Based on a total of 30 newly diagnosed patients throughout the whole time period, we calculated an incidence of 0.4 (prior to 2008) and 0.8 (from 2009), respectively, and a prevalence of 3.3 (overall, range 1-18) and 5.2 (from 2009, range 7-18), respectively, per 1 million inhabitants. Approximated current numbers for incidence and prevalence would be 68 and 431, respectively, for the entire region of Germany with 82.8 million inhabitants.

We sought to validate our data in a second, independent ECNM center (University Hospital Aachen, Germany) covering approximately 555,000 inhabitants. Calculated current numbers (2013-2018) for incidence and prevalence are 0.9 and 7, respectively, per 1 million inhabitants, corresponding to an incidence and prevalence of around 75 and 597 for the entire region of Germany. Figure 1 depicts all analyzed patients from Aachen (blue) and Mannheim (red).

Overall survival in various subgroups. Age was a risk factor for inferior survival. Median Overall survival (OS) in ASM, SM-AHN and MCL ± AHN was 'not reached', 3.3 years, and 2.6 years, respectively. OS in male patients was significantly shorter as compared to female patients (2.6 vs. 4.2 years from diagnosis of advSM, p=0.019; 3.5 vs. 10.5 years from diagnosis of SM, p=0.039).

Patients were classified according to the recently published mutation-adjusted risk score for advSM (MARS)[14]: a validated, five-parameter (one point each for: age>60, hemoglobin<10g/dl, platelets<100x10^9/l, presence of 1 *S*/*A*/*R* mutation, presence of >1 *S*/*A*/*R* mutation) WHO-independent prognostic score that defines three risk groups (low risk, 0-1 points; intermediate risk, 2 points; high risk, 3-5 points) for patients with advSM. The relative proportion of MARS low-risk (23/104, 22% vs. 10/22, 45%) and MARS high-risk patients (56/104, 54% vs. 7/22, 32%, p=0.026) and the median OS (3.1 years vs. not reached, p=0.015, data not shown) was significantly different between patients with *de novo* advSM and patients with progression from "ISM". In the latter cohort, *S*/*A*/*R* positive patients had less frequent hematological C-findings (42% vs. 60%; Table 2) but OS was still inferior compared to *S*/*A*/*R* negative patients.

Concurrent solid cancer. In 32/140 (23%) patients, a variety of preceding solid cancers were diagnosed in the skin (basalioma, n=4; melanoma n=2; epithelial cancer, n=1), urogenital tract (prostate cancer, n=6, renal cell carcinoma, n=4; urothelial carcinoma, n=2; seminoma n=1), gastrointestinal tract (gastric cancer, n=2; colorectal cancer, n=2; cholangiocarcinoma, n=1) or breast (n=4). During follow-up, one patient each developed a MC sarcoma, a cholangiocarcinoma and a non-Hodgkin lymphoma. Incidence of solid cancer was not increased as compared to an age-matched population.

Discussion

In adult patients, SM is characterized by variable MC infiltration in the BM accompanied by an almost invariable involvement of visceral organs. A *KIT* D816 mutation, most frequently D816V, is present in >90% of all patients with SM, whereas an elevated serum tryptase is measurable in >80% of patients with ISM and in almost all patients with advSM [6, 22, 23]. However, despite a broad availability of these diagnostic markers, our data suggest that the diagnosis of advSM is critically delayed in at least 30-40% of patients and is likely to be completely overlooked in a significant proportion of patients unless cases are referred to a specialized center [24]. Whereas ISM and MCL are relatively easy to recognize and to differentiate, based on the extent of low/high BM MC infiltration and low/high serum tryptase, respectively, the diagnosis of SM-AHN remains most problematic and controversial.

SM-AHN is basically characterized by multilineage involvement of the *KIT* D816V mutation through which the mutation can be identified at variable frequencies in all myeloid lineages, most frequently in monocytes and eosinophils, but potentially also in erythropoiesis, megakaryopoiesis and even lymphopoiesis [5, 25-28]. In addition, the vast majority of patients with SM-AHN are positive for additional somatic mutations, e.g., in the *S*/*A*/*R* gene panel, otherwise also found in related myeloid neoplasms such as CMML or MDS/MPN, acting as very strong adverse prognostic markers[12-14]. SM-AHN can therefore present with individually highly variable combinations of low or high BM MC burden, low or high levels of serum tryptase and low or high levels of multilineage and multimutated involvement, most frequently of monocytes and eosinophils. Without staining of BM biopsy slides for tryptase or CD117 (KIT) and in the absence of testing for serum tryptase and/or *KIT* D816V, SM is overlooked in at least 5%, probably up to 10% of patients and particularly in those with CMML, MDS/MPN or CEL-NOS/MPN with eosinophilia. Finally, skin lesions are often absent in advSM. All these issues and caveats can explain why advSM, especially SM-AHN is often overlooked or diagnosed with a substantial delay.

In our series, diagnosis of SM was initially missed in 20% of patients who were primarily diagnosed with one of these myeloid neoplasms for a median of 2 years. An interesting observation was that in the cohort of advSM patients with a history of ISM and suspected progression into advSM, an individually variable presence of monocytosis, eosinophilia, high *KIT* D816V EAB in PB and/or even mutations in the *S*/*A*/*R* gene was identified. Every patient in this cohort had at least one of these features, thus clearly suggesting the presence of SM with multilineage involvement or even as yet unrecognized (early) advSM rather than typical ISM. The significant difference in overall survival between *S*/*A*/*R* positive *de novo* advSM and *S*/*A*/*R* positive secondary advSM is based upon the significantly higher frequency of relevant C-findings and consequently higher proportion of high-risk patients according to the "Mutation Associated Risk Score (MARS)" in *S*/*A*/*R* positive *de novo* advSM patients.

The incidence and prevalence of advSM is unclear due to the rarity of this disorder [17, 18]. Having the status of an ECNM center, our national registry and the availability of clinical trials have led to referral of >500 SM patients within the last 10 years and formed the basis for our epidemiologic studies on 140 patients with advSM. Because the origin of the 140 patients was very heterogeneous, with significantly fewer patients coming from northern and eastern Germany, and because it could be argued that data are biased because of referral of non-local patients to specialized centers, we primarily focused our calculations on incidence and prevalence of advSM on two restricted local areas with 2.4 million (MPRN) and 0.55 million (Aachen City region, AAR) inhabitants, respectively, directly surrounding the ECNM centers in Mannheim and Aachen. A possible explanation for the lower incidence but higher prevalence in AAR may be a lower number of high-risk patients in the Aachen cohort, best proven by a lower proportion of *S*/*A*/*R* positive patients as compared to the Mannheim cohort (3/17, 18% vs. 71/123, 58%). In addition, less frequent thorough diagnosis and referral of older/frail patients may also add to an underestimation of the real

incidence of advSM. Nonetheless, the incidence and prevalence have constantly risen in both areas, while numbers are significantly lower in regions without such centers.

In addition, this series revealed even more relevant data on disease characteristics and epidemiologic aspects. Apart from AHN, concomitant hematologic or solid malignancies were present in 23% of patients, which is higher than the 10% of patients recently reported [29]. Five patients had two or even more simultaneous or consecutive malignancies apart from SM and AHN, suggesting potential predisposition for development of various hematologic and/or solid neoplasms in those five patients. However, incidence of solid cancer in general was not increased in the SM cohort as compared to an age-matched population.

But which factors have contributed to the improved disease awareness, when BM histology and serum tryptase have otherwise already been available for several years? The first major step forward was the broad availability of qualitative and quantitative PCR techniques for identification of mutations in *KIT*, most importantly *KIT* D816V. Quantitative PCR at DNA (variant allele frequency, VAF) or RNA/cDNA (expressed allele burden, EAB) level, if routinely available, allows rapid diagnosis of SM, decisively supporting adequate subclassification and allowing monitoring of disease response[6, 30, 31]. The second major step forward was the observation of responses of advSM on KIT inhibitors such as midostaurin, and more recently, avapritinib or ripretinib[32]. Thirdly, the prognostic relevance of next generation sequencing-based identification of additional somatic mutations has shown the strong relationship between SM and various other myeloid neoplasms, with somatic mutations such as *S*/*A*/*R* representing the genetic complexity and prognostic relevance while *KIT* mutations influence phenotype and disease burden[12, 13, 33]. The annual meetings of the ECNM may also have contributed to increased awareness and education of young colleagues. Finally, the establishment of national (e.g. Germany Registry on Eosinophils and Mast Cells)

and European (ECNM) registries was of pivotal importance, and has also attracted non-European partners[34].

We conclude that i) disease awareness has constantly risen through establishment of registries and the availability of new therapeutic options, ii) incidence and prevalence of advSM is significantly higher than currently appreciated and the detection rate is highest in areas with specialized centers, iii) prognosis is inferior in male vs. female patients and in *de novo* vs. secondary advSM, and iv) beside estimation of BM MC infiltration and serum tryptase, the qualitative and quantitative assessment of the *KIT* D816V EAB or VAF and additional somatic mutations in patients with SM(-AHN) and all related myeloid neoplasms are of utmost importance for reliable diagnosis, subclassification and prognostication of SM.

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Table 1: Patient characteristics

	n	Age, median (range)	Serum tryptase level, median (range)	*KIT* D816 positive, *n*
ASM	9	65 (27-78)	211 (80-561)	9
SM-AHN	105	69 (26-87)	132 (5-951)[#]	104
MCL	9	63 (47-75)	628 (193-1,690)	7[*/**]
MCL-AHN	17	68 (48-86)	371 (61-1,675)	16[*/**]

* *KIT* D816Y, ***KIT* D816H

[#] normal serum tryptase level in 7 patients (5%)

ASM: aggressive systemic mastocytosis, SM-AHN: systemic mastocytosis with associated hematologic neoplasm, MCL: mast cell leukemia;

Table 2: clinical and laboratory parameters in advSM patients with and without history of indolent systemic mastocytosis

	Progression of "ISM" to advSM/misdiagnosis of AdvSM		*De novo* advSM	
NGS	22/23		104/117	
S/A/R	negative	positive	negative	positive
Number of patients (%)	12 (57%)	10 (43%)	40 (45%)	64 (55%)
SM-AHN	7	10	32	62
Median time (years) to diagnosis of advSM (range)	5.2 (0.7-38)	2.3 (0.2-13)	NA	NA
C-findings				
Hemoglobin, g/dl; median(range)	12.5 (9.8-15.1)	11.3 (9.2-14.3)	11.1 (5.8-16)	10.7 (6.5-14.2)
<10g/dl, *n* (%)	1 (8)	2 (20)	15 (38)	28 (44)
Platelets, x10^9/l; median (range)	200 (83-441)	123 (18-308)	170 (12-993)	95 (12-795)
<100 x10^9/l, *n* (%)	3 (25)	3 (30)	15 (38)	34 (53)
Albumin level, g/l; median (level)	40 (24-45)	38 (32-46)	39 (22-58)	35 (19-48)
<30g/l, *n* (%)	1 (8)	0 (0)	4 (10)	7 (11)
Alkaline phosphatase, U/l; median (range)	99 (55-511)	176 (49-621)	127 (50-640)	259 (54-1206)
>126 U/l, *n* (%)	4 (33)	6 (60)	18 (45)	51 (80)
B-findings				
Serum tryptase level, µg/l; median (range)	194 (61-1030)	335 (41-952)	124 (5-1690)	187 (24-1675)
>200µg/l, *n* (%)	5 (42)	7 (70)	14 (35)	29 (45)
Splenomegaly, *n* (%)	12 (100)	8 (80)	30 (75)	55 (86)
Ascites, *n* (%)	4 (33)	6 (60)	10 (25)	31 (48)
Additional SM and/or AHN relevant findings				
KIT D816V AB in PB, %; median (range)	28 (12-77)	45 (0-74)	19 (0-67)	31 (0-74)
Leukocytes, x10^9/l; median (range)	8.2 (3.6-19.3)	9.8 (4.4-66)	11.4 (2.4-89.8)	8.7 (1.3-123.5)
Eosinophils, x10^9/l; median (range)	0.3 (0.0-1.3)	0.9 (0.0-13.2)	0.3 (0.0-16.3)	0.4 (0.0-100)
>1x10^9/l, *n* (%)	3 (25)	3 (30)	8 (20)	20 (31)
Monocytes, x10^9/l; median (range)	0.5 (0.2-2.7)	1.2 (0.4-3.8)	0.6 (0-4.1)	1.1 (0.07-17.9)
>1 x10^9/l, *n* (%)	3 (25)	5 (50)	9 (23)	32 (50)
Outcome				
MARS:				
Low, *n* (%)	9 (75)	1 (10)	23 (58)	0 (0)
Intermediate, *n* (%)	2 (17)	3 (30)	12 (30)	13 (20)
High, *n* (%)	1 (8)	6 (60)	5 (12)	51 (80)
Median overall survival (years)	NR	5.7	10.5	2.5

AB: allele burden; advSM: advanced systemic mastocytosis; ISM: indolent systemic mastocytosis; MARS: mutation-adjusted risk score in advSM; NA: not applicable; NGS: next generation sequencing; NR: not reached;

NA: not applicable; PB: peripheral blood; *S/A/R*: *SRSF2*/*ASXL1*/*RUNX1*; SM-AHN: systemic mastocytosis with an associated hematologic neoplasm

445
446

Figure Legend

Figure 1: Place of residence of all patients with advSM who were referred to Aachen or Mannheim between 2003 and 2018.

Figure 2a: Cumulative frequencies of newly diagnosed advSM patients in Mannheim and Aachen 2003-2018. *=patients; AAR= Aachen city region, MPRN= Metropolitan Region Rhein Neckar

Figure 2b: Cumulative frequencies of advSM patients being treated in Mannheim and Aachen 2003-2018

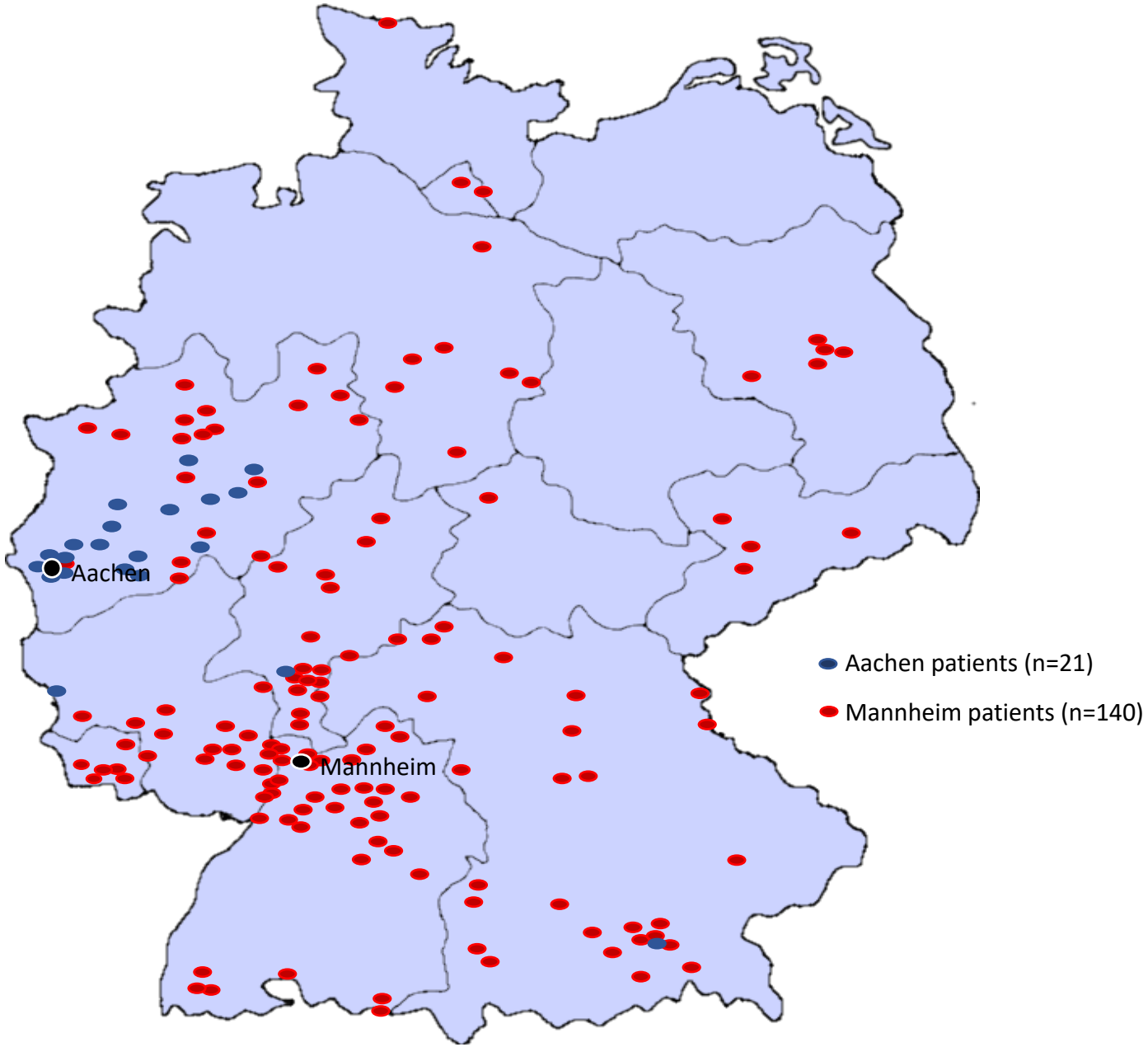


Figure 1 place of residence of all patients with advanced SM who presented at Aachen or Mannheim between 2003 and 2018

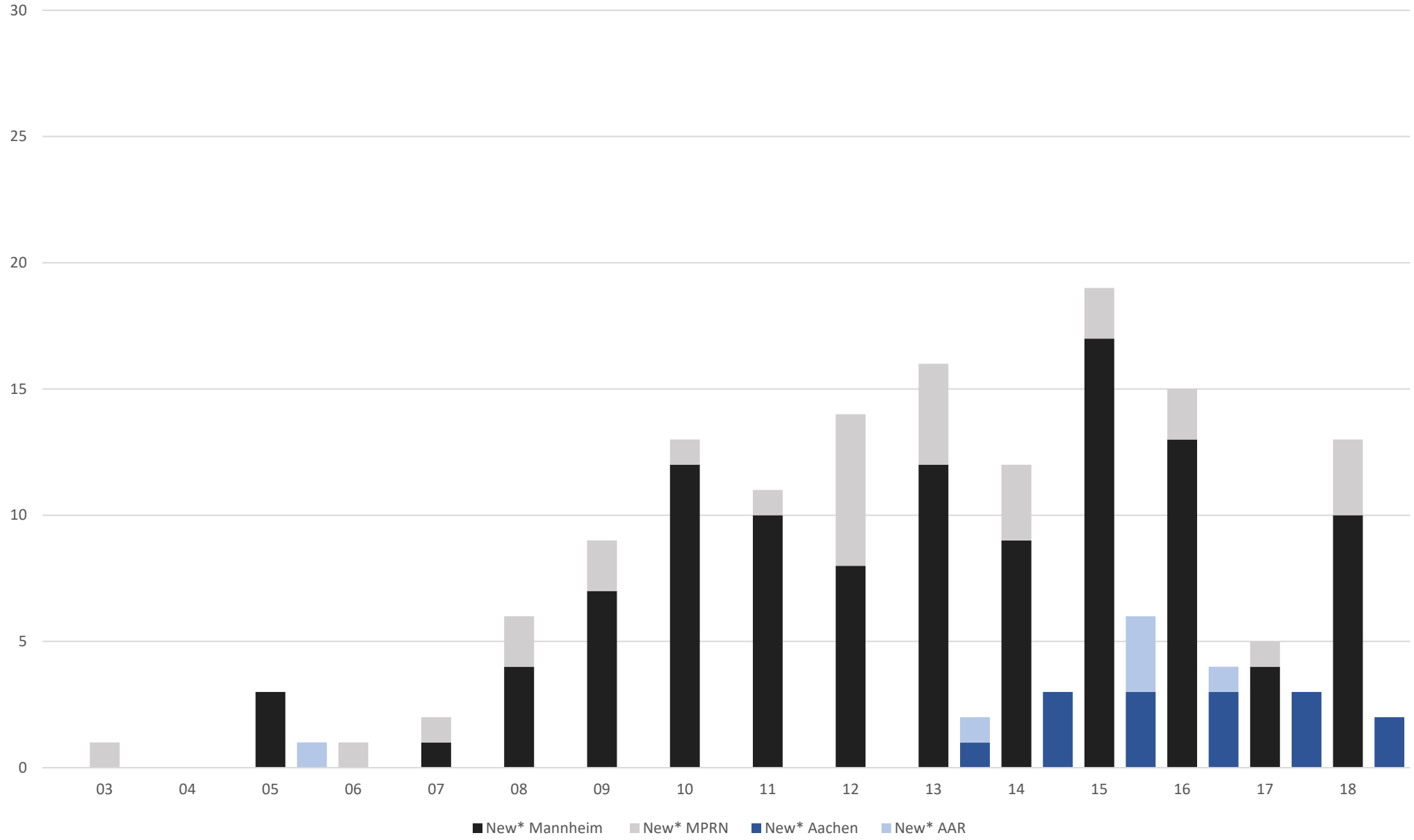
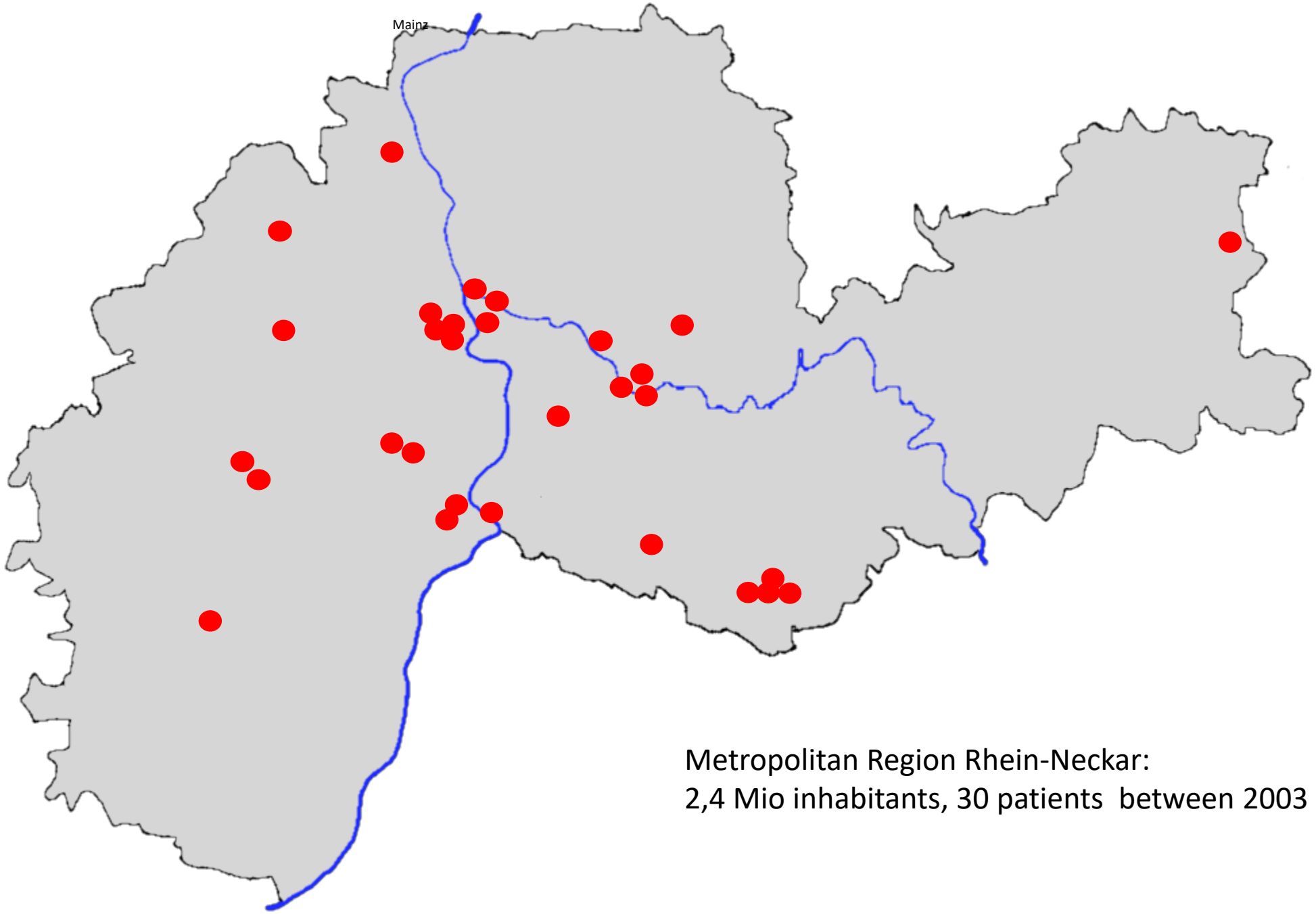


Figure 2a: cumulative frequencies of newly diagnosed advSM patients in Mannheim and Aachen 2003-2018



Metropolitan Region Rhein-Neckar:
2,4 Mio inhabitants, 30 patients between 2003 and 2018

Supplementary Figure 1: Map of the Metropolitan Region Rhein-Neckar (MPRN) delineating the origin of 30 patients from that area

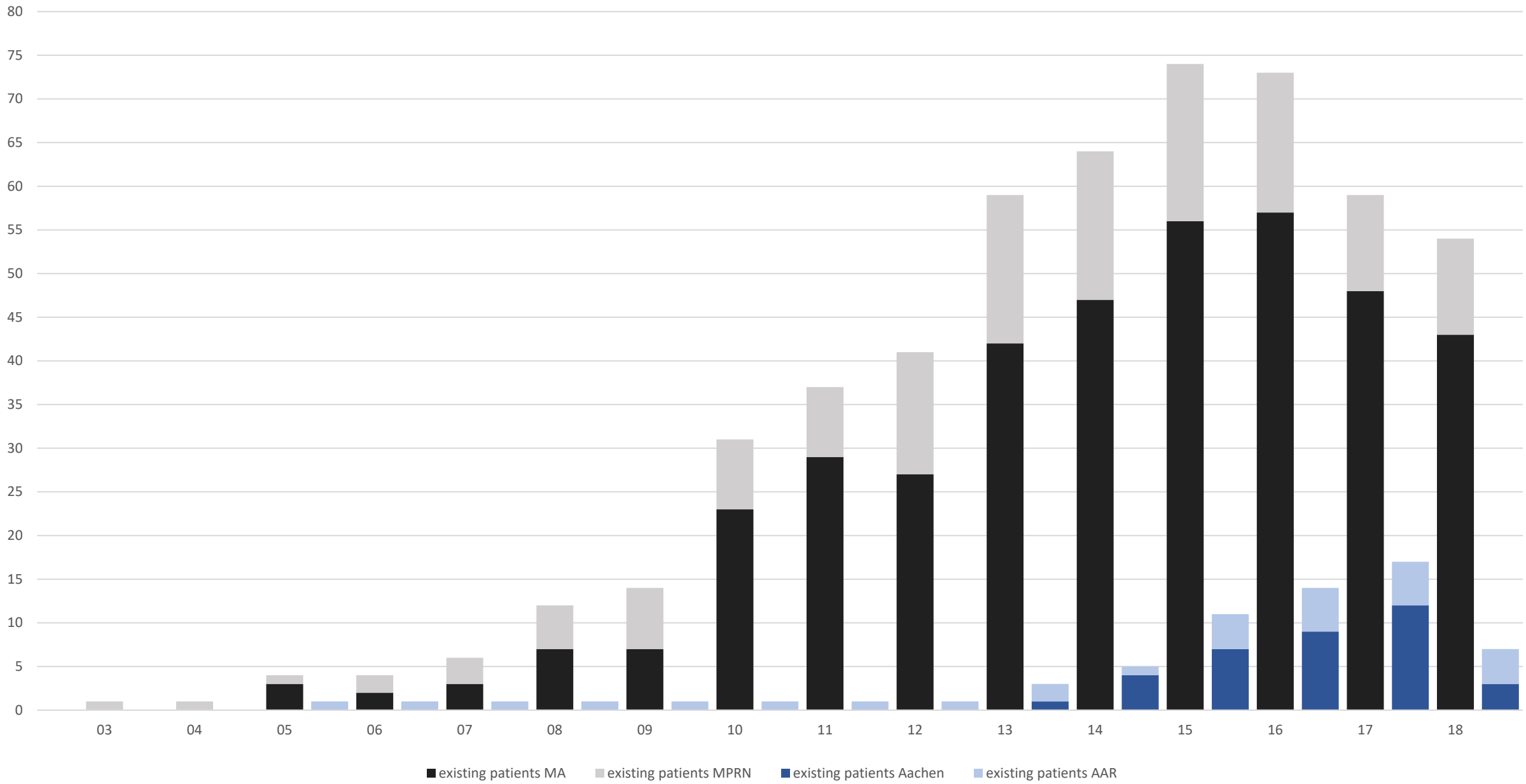


Figure 2b: cumulative frequencies of advSM patients being treated in Mannheim and Aachen 2003-2018