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Historic characteristics and mortality of patients in the Swiss Amyloidosis Registry

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Summary

AIMS OF THE STUDY: Systemic amyloidoses are rare protein-folding diseases with heterogeneous, often non-specific clinical presentations. To better understand systemic amyloidoses and to apply state-of-the-art diagnostic pathways and treatment, the interdisciplinary Amyloidosis Network was founded in 2013 at University Hospital Zurich. In this respect, a registry was implemented to study the characteristics and life expectancy of patients with amyloidosis within the area covered by the network. Patient data were collected retrospectively for the period 2005–2014 and prospectively from 2015 onwards.

METHODS: Patients aged 18 years or older diagnosed with any subtype of systemic amyloidosis were eligible for inclusion if they were treated in one of the four referring centres (Zurich, Chur, St Gallen, Bellinzona). Baseline data were captured at the time of diagnosis. Follow-up data were assessed half-yearly for the first two years, then annually.

RESULTS: Between January 2005 and March 2020, 247 patients were screened, and 155 patients with confirmed systemic amyloidosis were included in the present analysis. The most common amyloidosis type was light-chain (49.7%, n = 77), followed by transthyretin amyloidosis (40%, n = 62) and amyloid A amyloidosis (5.2%, n = 8). Most patients (61.9%, n = 96) presented with multiorgan involvement. Nevertheless, single organ involvement was seen in all types of amyloidosis, most commonly in amyloid A amyloidosis (75%, n = 6).

The median observation time of the surviving patients was calculated by the reverse Kaplan-Meier method and was 3.29 years (95% confidence interval [CI] 2.33–4.87); it was 4.87 years (95% CI 3.14–7.22) in light-chain amyloidosis patients and 1.85 years (95% CI 1.48–3.66) in transthyretin amyloidosis patients, respectively. The 1-, 3- and 5-year survival rates were 87.0% (95% CI 79.4–95.3%), 68.5% (95% CI 57.4–81.7%) and 66.0% (95% CI 54.6–79.9%) respectively for light-chain amyloidosis patients and 91.2% (95% CI 83.2–99.8%), 77.0% (95% CI 63.4–93.7%) and 50.6% (95% CI 31.8–80.3%) respectively for transthyretin amyloidosis patients. There was no significant difference between the two groups (p = 0.81).

CONCLUSION: During registry set-up, a more comprehensive work-up of our patients suffering mainly from light-chain amyloidosis and transthyretin amyloidosis was implemented. Survival rates were remarkably high and similar between light-chain amyloidosis and transthyretin amyloidosis, a finding which was noted in similar historic registries of international centres. However, further studies are needed to depict morbidity and mortality as the amyloidosis landscape is changing rapidly.

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Introduction

The term “amyloidosis” refers to a heterogeneous group of diseases with typical histopathological features defined as tissue deposition of insoluble proteins and consequent organ dysfunction [1, 2]. To date, more than thirty different proteins are known to be amyloidogenic [3]. The most common types include immunoglobulin light-chain amyloidosis due to an underlying haematological disorder, transthyretin amyloidosis in which wild-type and hereditary variant forms are distinguished, and amyloid A amyloidosis due to chronic inflammatory processes. Although

organ tropism and hence clinical manifestations may differ between the various protein subtypes, there are nevertheless some common clinical features such as heart failure, nephropathy and peripheral neuropathy [2]. Most of these symptoms are not specific to amyloidosis, but can also occur with common diseases such as diabetes mellitus or hypertension. Therefore, the diagnosis of systemic amyloidosis is challenging, and treatment initiation often delayed [4]. Diagnostic work-up of patients with suspected amyloidosis must allow unambiguous characterisation of the amyloid subtype and should provide information about the spectrum and extent of organ involvement.

With rare diseases such as these, which present with a variety of symptoms, the path to correct diagnosis and the choice of optimal treatment is a challenge. Systemic amyloidosis is therefore a prototypical disease entity that requires an interdisciplinary diagnostic and and therapeutic approach [5].

Until recently, there have been little epidemiological data on systemic amyloidosis in Switzerland. Therefore, in 2013, the Collaborative Amyloidosis Network Zurich was founded at University Hospital Zurich (USZ) as the first network of its kind in Switzerland. It brings together specialists in haematology/oncology, cardiology, nephrology, pathology, neurology, medical genetics, rheumatology and gastroenterology, in order to improve and standardise the diagnostic work-up and treatment of these often critically ill patients with rare diseases.

It has long been recognised that medical registries do not just provide basic epidemiological data, but contribute to better understanding of mechanisms of disease within specific healthcare systems, ultimately resulting in better medical outcomes, especially in rare diseases for which randomised controlled trials are scarce [6]. Therefore, one of the central pillars of the network is the Swiss Amyloidosis Registry, a patient registry that collects data for all types of systemic amyloidosis. The objective of the present study was to describe the epidemiological pattern of systemic amyloidosis in Switzerland and to study patient outcomes in the different amyloidosis subtypes.

Materials and methods

Patients have been included since 2005. Patient data were collected retrospectively for the period 2005 to 2014 and prospectively from 2015. The cut-off date for the current data analysis is February 2020. Screening of eligible patients was performed locally; data monitoring was performed centrally at University Hospital Zurich.

Inclusion criteria

Patients 18 years or older diagnosed with any subtype of systemic amyloidosis were eligible for inclusion if they had been or were being treated in one of the four referring centres (USZ; Graubunden cantonal hospital [KSGR]; the oncological institute of southern Switzerland [IOSI]; St Gallen cantonal hospital [KSSG]). Patients with any form of amyloidosis were included in the analysis, except those with localised amyloidosis. Written informed consent was required from either the patient or, if deceased, his/her next of kin prior to inclusion in the registry. The local ethics committee approved the study (KEK-ZH-NR 2014-0490 / PB_2016_01744), but did not allow for inclusion of patients without written informed consent, if they were lost to follow-up, and/or could not be followed due to changes of address or death.

Diagnosis of systemic amyloidosis required direct or indirect proof of organ involvement, as well as one or more of the following features: (a) a positive biopsy with typical birefringence of a Congo red-stained specimen under polarised light, and/or (b) the presence of a known amyloidogenic mutation, and/or (c) non-biopsy-proven diagnosis of cardiac transthyretin amyloidosis by scintigraphy [7, 8].

Amyloid subtyping was performed locally by immunohistochemistry, generally by using commercially available antibodies. After the Collaborative Amyloidosis Network was founded in 2013, the tissue samples of inconclusive cases were sent for external review, mostly by the German reference pathology centre (Prof. Röcken, Kiel, Germany). If the diagnosis remained inconclusive, the Amyloidosis Research and Treatment Center Pavia, Italy, was contacted for evaluation using mass spectrometry (MS)-based proteomics analysis [9, 10]. The Institute of Medical Genetics at the University of Zurich performed routine genetic testing.

Data capture and electronic case report forms

Primary data were extracted locally from the electronic and non-electronic patient charts and entered into electronic case report forms in SecuTrial®. SecuTrial® is a web-based application allowing access by authorised personnel at all participating centres. A unique patient ID number was computer-generated upon data entry. The information linking patient name to Study ID (key) was printed and stored locally separate from all other data. Accuracy and completeness of the data were analysed centrally at University Hospital Zurich.

Baseline data were captured at the time of diagnosis (± 3 months). Baseline data consisted of approximately 300 parameters including personal medical history, symptoms leading to diagnosis, demographic data and other data (see electronic case report forms available as supplementary file for download at https://doi.org/10.57187/s.3485). Organ involvement was defined as biopsy-proven amyloid deposition in the respective organ (or tissue) and/or typical organ alterations as defined by the working group for light-chain and transthyretin amyloidosis [7, 11]. Follow-up data were assessed half-yearly for the first two years then annually. The follow-up data included, among others, pharmacological and non-pharmacological treatment, changes in organ function and laboratory values (see electronic case report forms).

Statistical analyses were performed with IBM SPSS 28.010 (IBM, Armonk, New York, USA) and R statistics version 4.1.3. Survival analysis was performed by the Kaplan-Meier method and compared using the log rank test. The median observation time was estimated by the inverse Kaplan-Meier method [12].

Results

Between 1 January 2005 and 29 February 2020, 247 patients were screened, and 155 patients with confirmed systemic amyloidosis were included in the present analysis

(figure 1): 69 and 86 in the retrospective and prospective cohorts, respectively.

Overall, the most common amyloidosis type was light-chain amyloidosis (49.7%, n = 77), followed by transthyretin amyloidosis (40%, n = 62) (25.8%, n = 40 wild-type transthyretin amyloidosis and 8.4%, n = 13 hereditary transthyretin amyloidosis); in 5.8%, n = 9, transthyretin gene (*TTR*) mutation analysis was not performed. Amyloid A amyloidosis accounted for 5.2%, n = 8. In some of the patients (4.5%, n = 7), subtyping was not productive. Concomitant transthyretin and light-chain amyloidosis was present in one patient (0.6%).

Mean age at diagnosis was 64.7 years (median 68.2 years, range 18.6–85) with a predominance of males (76%, n = 118; light-chain amyloidosis n = 55, transthyretin amyloidosis n = 54, amyloid A amyloidosis n = 4, unclear n = 5). Patients were included from the four centres (USZ, KSGR, IOSI, KSSG). Most patients originated from Switzerland (63%, n = 98), followed by Italy (11%, n = 17) and Portugal (4%, n = 6).

Diagnosis was made by tissue biopsy in 87.8% (n = 136) of patients and by a non-biopsy approach by scintigraphy in 10.3%, n = 16 (transthyretin amyloidosis patients) [8]; in 3 patients, data were missing. The most common biopsy sites were the heart (n = 49), kidney (n = 39), gastrointestinal tract (n = 38), abdominal fat tissue aspirate (n = 46), skin (n = 4) and lung (n = 3). One site was biopsied in 52.3% (n = 71; transthyretin amyloidosis n = 32, light-chain amyloidosis n = 39) of patients, two sites in 25.8% (n = 40) patients and three sites in 9% (n = 14) patients. In 5.2% (n = 8) patients, amyloid was found in the bone marrow biopsy. Notably not all bone marrow biopsies were routinely stained with Congo red.

In 54.8% of transthyretin amyloidosis patients (n = 34), an endomyocardial biopsy was done to establish the diagnosis. In light-chain amyloidosis patients, the most common site of biopsy was the kidney (39%, n = 30), followed by the gastrointestinal tract (19.5%, n = 15) and the heart (16.9%, n = 13). In 9.1% of light-chain amyloidosis patients (n = 7), diagnosis was established with abdominal fat aspirate only.

Organ involvement was defined by either proven amyloid in organ biopsy, elevated biomarkers or typical symptoms such as weight loss, nausea, diarrhoea or constipation, polyneuropathy, orthostatic dysregulation, erectile dysfunction in absence of other causes.

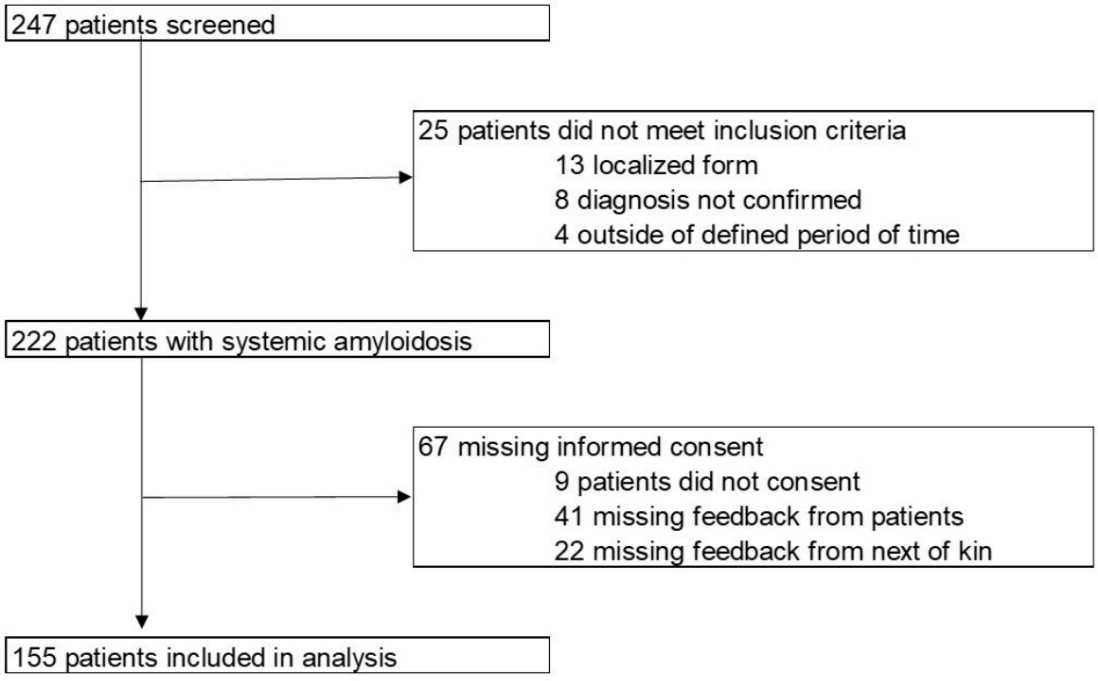
Most patients (61.9%, n = 96) presented with multiorgan involvement with typical tropism determined by the amyloidosis type. However, single organ involvement was seen in all types of amyloidosis (n = 56, 36.1%; wild-type transthyretin amyloidosis n = 16/40, 40%; hereditary transthyretin amyloidosis n = 2/13, 15.3%; light-chain amyloidosis n = 22/77, 28.6% and amyloid A amyloidosis n = 6/8, 75%).

The number of patients with transthyretin and light-chain amyloidosis in our registry increased over time. From 2011, the numbers of diagnosed transthyretin amyloidosis patients increased rapidly (figure 2).

Light-chain amyloidosis

Of the 77 patients with light-chain amyloidosis, free light chains were found in 57.1% (n = 44), IgG in 28.6% (n = 22), IgM in 9.1% (n = 7) and IgA in 5.2% (n = 4). Light-chain lambda was present in most of the patients (70.1%; n = 54). Translocation t(11;14) was found in 27.3% (n = 21). In 53.2% (n = 41) of the patients, FISH analysis was not performed (30 in the retrospective cohort, 11 in the prospective cohort).

Figure 1: Patients included in the analysis.



Patients who were included in our registry were staged according to the revised Mayo staging system [11]. Stage 1, 2, 3 and 4 were present in 10.3%, n = 8, 22.1%, n = 17, 13%, n = 10 and 16.9%, n = 13, respectively. 37.7%, n = 29 patients could not be staged due to missing data (22 in the retrospective cohort, 7 in the prospective cohort).

Plasma cell infiltration grade was ≥10% in 62.3% (n = 48) and <10% in 24.7% (n = 19). In 13% (n = 10, 9 in retrospective cohort), the infiltration grade was not known.

Table 1:
Baseline characteristics.

		Light-chain amyloidosis	Transthyretin amyloidosis, wild-type	Transthyretin amyloidosis, variant	Transthyretin amyloidosis without genetic testing	Amyloid A amyloidosis
Age (yrs)	Mean ± SEM	63.3 ± 1.3	73.1 ± 1.4	43.2 ± 4.5	77.1 ± 1.6	46.2 ± 6.2
	Range	38.3–84.9	51.4–84.9	18.6–73.2	68.2–84.3	24.7–76.4
	Data available for n°/total cases	77/77	40/40	12/13	9/9	8/8
Male sex	n (%)	54 (70%)	38 (95%)	7 (53%)	9 (100%)	4 (50%)
BMI (kg/m^2)	Mean ± SEM	25.4 ± 0.5	27.1 ± 0.6	24.2 ± 1.5	28.4 ± 2.9	25 ± 2.3
	Range	17.8–36	18.3–37	18.7–36	22–39	21.8–36.6
	Data available for n°/total cases	69/77	40/40	11/13	5/9	4/8
Number of organs involved, n° (%)	0	0	0	1 (7.7%) *	0	0
	1	22 (28.6%)	16 (40%)	2 (15.4%)	5 (55.5%)	6 (75%)
	2	30 (38.9%)	21 (52.5%)	5 (38.5%)	3 (33.3%)	1 (12.5%)
	3	13 (16.9%)	3 (7.5%)	2 (15.4%)	1 (11.1%)	1 (12.5%)
	≥4	12 (15.6%)	0	2 (15.4%)	0	0
	Unknown	0	0	1 (7.7%)	0	0
Involved organs, n° (%)	Heart	55 (71.4%)	38 (95%)	7 (53.8%)	9 (100%)	1 (12.5%)
	Kidney	46 (59.7%)	0	1 (7.7%)	1 (11.1%)	7 (87.5%)
	GI	22 (28.6%)	2 (5%)	1 (7.7%)	0	1 (12.5%)
	Liver	6 (7.8%)	2 (5%)	0	0	0
	Nerve	18 (23.4%)	5 (12.5%)	11 (84.6%)	0	1 (12.5%)
	Soft tissue	15 (19.5%)	2 (5%)	1 (7.7%)	0	1 (12.5%)
	Carpal tunnel syndrome	8 (10.4%)	23 (57.5%)	6 (46.2%)	4 (44.4%)	0
NT-pro BNP (ng/l)	Mean ± SEM	4433 ± 990	2913 ± 587	1153 ± 512	3851 ± 1288	10657
	Range	81–44085	46–18143	24–3710	527–6748	(one value)
	Data available for n°/total cases	66/77	38/40	7/13	4/9	1/8
Troponin T (ng/l)	Mean ± SEM	41 ± 5.1	218 ± 162	41 ± 28	36 ± 10	NA
	Range	0–166	11–4578	5–152	26–46	
	Data available for n°/total cases	51/77	28/40	5/13	2/9	0/8
Creatinine (µmol/l)	Mean ± SEM	109 ± 6	118 ± 19	98 ± 16	101 ± 14	132 ± 32
	Range	52–282	52–832	54–173	51–140	79–188
eGFR (ml/min)	Mean ± SEM	66 ± 3	67 ± 3	82 ± 13	65 ± 9	50 ± 14
	Range	22–111	5–104	40–140	43–101	22–70
	Data available for n°/total cases (creatinine and eGFR)	72/77	39/40	8/13	6/9	3/8
eGFR ≤30 or dialysis, n° (%)		8 (10%)	2 (5%)	0	0	2 (25%)

BMI: body mass index; eGFR: estimated glomerular filtration rate; SEM: standard error of the mean.

*asymptomatic carrier

Table 2:
Organ involvement of the most common types of amyloidosis.

Type	n	Number of organs, median	Heart	Kidney	GI	Liver	PNS/ANS	CTS	Lung
Light-chain amyloidosis	77	1.5 (0–3)	+++	++	+	+	+	+	–
Transthyretin amyloidosis, wild-type	40	1.5 (0–3)	+++	–	–	–	+	++	–
Transthyretin amyloidosis, variant	13	1 (0–2)	++	+	+	–	+++	++	–
Amyloid A amyloidosis	8	1.3 (1–3)	+	+++	+	–	+	–	–

CTS: carpal tunnel syndrome; GI: gastrointestinal tract; PNS/ANS: peripheral nervous system / autonomic nervous system;

–: 0–5%; +: 6–35%; ++ 36–70%; +++: 71–100%.

Transthyretin amyloidosis

Of all transthyretin amyloidosis patients, 87.1% (n = 54) had cardiac involvement. Overall, 53.2% (n = 33) presented with Gillmore stage 1, 16.1% (n = 10) with stage 2 and 9.7% (n = 6) with stage 3. In 21% (n = 13; n = 5 in the retrospective cohort), the Gillmore stage could not be determined [13].

In 22.6% (n = 14) patients, concomitant monoclonal gammopathy of undetermined significance (MGUS) was found; in 11.3%, n = 7 patients (n = 5 from the retrospective cohort), gammopathy screening was not done. 56.5% (n = 35) of the patients suffered from carpal tunnel syndrome, 14.5% (n = 9) from lumbar spinal stenosis.

In the retrospective cohort, the main trigger for genetic testing was neurological symptoms or a positive family history. In the prospective cohort, testing was recommended in all newly admitted transthyretin amyloidosis patients, if cost coverage by the Swiss health insurance fund was guaranteed. Of the 62 patients with transthyretin amyloidosis, *TTR* mutation analysis was performed in 74% (n = 46). Variant transthyretin amyloidosis with an amyloidogenic mutation in *TTR* was detected in 13 patients (28%).

In patients with variant transthyretin amyloidosis, the following mutations were found: p.(Val50Met) (n = 5, Portuguese ancestry, 4 different families), p.(Ile127Met) (n = 3, Bosnian ancestry, 1 family), p.(Phe53Val) (n = 1, Macedonian ancestry), p.(Thr79Lys) (n = 1, Egyptian ancestry), p.(Thr80Ala) (n = 1, Swiss ancestry), p.(Val142Ile) (n = 2, Swiss ancestry, individuals unrelated).

p.(Val50Met), p.(Ile127Met), p.(Phe53Val) patients presented with a predominantly neurological phenotype, whereas p.(Thr79Lys), p.(Thr80Ala) and p.(Val142Ile) patients showed a predominantly cardiac phenotype.

Amyloid A amyloidosis

Of the 8 amyloid A amyloidosis patients, familial Mediterranean fever was the most common underlying disease (63%; n = 5), one patient had rheumatoid arthritis, one had Crohn's disease, one had an unknown disease.

Overall survival

The median observation time for surviving patients calculated by the reverse Kaplan-Meier method was 3.29 years (95% confidence interval [CI] 2.33–4.87); 4.87 years (95% CI 3.14–7.22) in light-chain amyloidosis patients and 1.85 years (95% CI 1.48–3.66) in transthyretin amyloidosis patients. 32% of the patients (n = 50) died during the observation period. The average age at death was 68.7 years (median 70.2 years, range 34.5–87.3 years).

The survival analysis for light-chain and transthyretin amyloidosis patients is shown in figure 3. 1-, 3- and 5-year survival rates were 87.0% (95% CI 79.4–95.3%), 68.5% (95% CI 57.4–81.7%) and 66.0% (95% CI 54.6–79.9%) respectively for light-chain amyloidosis patients and 91.2% (95% CI 83.2–99.8%), 77.0% (95% CI 63.4–93.7%) and 50.6% (95% CI 31.8–80.3%) respectively for transthyretin amyloidosis patients. There was no significant difference between the two groups (p = 0.81) (figure 3).

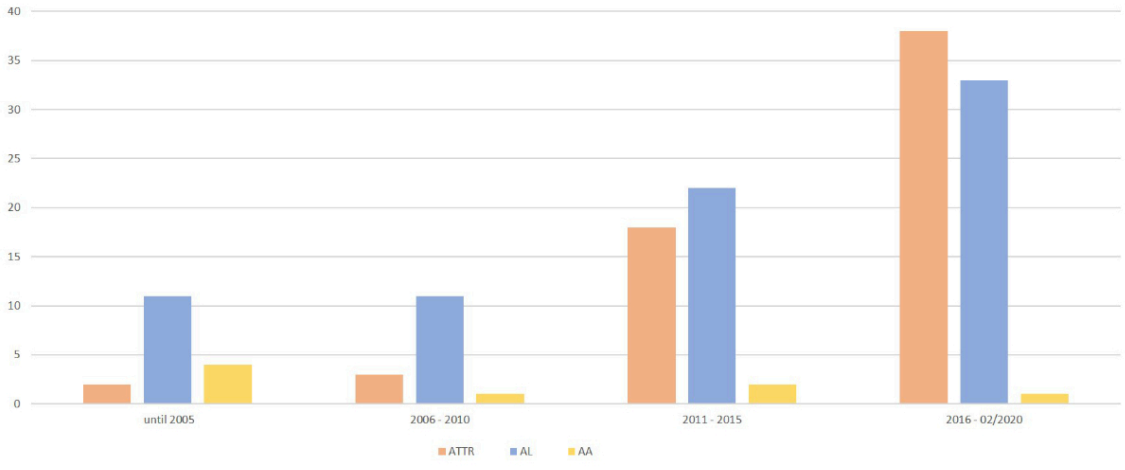
Discussion

General findings

We report here for the first time data from the Swiss Amyloidosis Registry on systemic amyloidosis. Our patients show a distribution of different amyloidosis subtypes consistent with data from the literature [14]. Light-chain amyloidosis and wild-type transthyretin amyloidosis account for most of the cases. The relatively high number (8%) of variant transthyretin amyloidosis in our patient cohort likely reflects our status as one of the two Swiss referral centres for RNA interference therapy such as Patisiran and Inotersen and as a tertiary referral centre with organ transplantation activity [15]. Our patient registry does not yet cover the whole of Switzerland, which should be the goal for a small country such as ours.

Most patients presented with cardiac or renal involvement. Clinically significant organ failure is almost always associated with advanced disease and unfavourable outcome [11, 13]. Therefore, efforts must be made to enable early diagnosis by raising awareness of these rare diseases and investigating suspected cases in a timely manner.

Figure 2: Number of amyloidosis patients included in the registry over time. ATTR: transthyretin amyloidosis; AL: light-chain amyloidosis; AA: amyloid A amyloidosis.



In transthyretin amyloidosis, the diagnosis was established mostly through tissue biopsy. A non-biopsy approach for transthyretin amyloidosis was considered in patients from 2016 onwards, as data revealed an excellent specificity and sensitivity of the semi-quantitative measurement of the cardiac tracer uptake in bone scintigraphy in patients in whom a monoclonal gammopathy has been ruled out [8, 13, 16].

Our data show an almost exponential increase in transthyretin amyloidosis within the Collaborative Amyloidosis Network since 2015, as experienced by other centres [17]. This is most likely due to increased awareness and better diagnostic pathways [18]. Patients with heart failure and preserved ejection fraction (HFpEF) within our network undergo systematic evaluation with echocardiography, MRI and, in case of absence of MGUS, bone scintigraphy to detect or rule out transthyretin amyloidosis [19]. We suspect that there will be a further shift towards wild-type transthyretin amyloidosis as the approval of new treatments increases awareness of the disease.

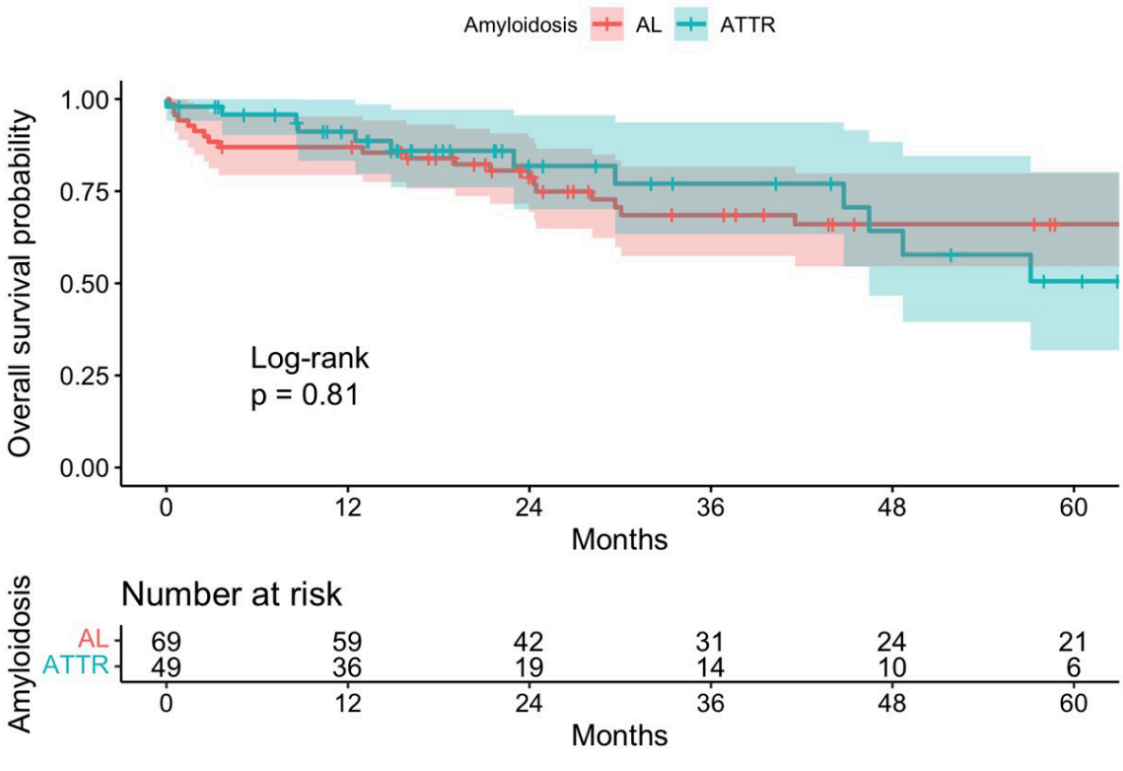
More than half of the patients with light-chain amyloidosis in our registry have a clonal plasma cell infiltration of ≥10% in bone marrow samples, as compared to 20–40% in patient cohorts reported in the literature [20, 21]. These patients have a comparatively high plasma cell burden and worse outcome compared to patients with light-chain amyloidosis and <10% bone marrow plasma cells [20]. We can only speculate on the reasons for this relatively high percentage of patients in our registry, but late diagnosis with expansion of the plasma cell clone might be an explanation. Diagnosis of light-chain amyloidosis is often delayed by more than one year from the onset of first symptoms and advanced disease is associated with unfavourable outcome [4]. In order to address the challenge of early disease detection, we included sensitive biomarkers of cardiac amyloidosis (NT-proBNP) and renal amyloidosis (albuminuria) in the regular follow-up of patients with MGUS and abnormal free light chain (FLC) ratio [22–24].

Of note, amyloid A amyloidosis patients were comparatively rare and mainly found in the retrospective patient cohort. This phenomenon has been described by others, and is due to earlier diagnosis of predisposing conditions for amyloid A amyloidosis as well as widespread access to more effective treatments for inflammatory and infectious diseases [25, 26].

In our cohort, overall survival of patients with light-chain amyloidosis is better than described in the literature. This is probably due to a selection bias as the ethics committee only permitted retrospective inclusion of deceased patients in the registry with informed consent of a next of kin. In the transthyretin amyloidosis cohort, the median overall survival of around 5 years reflects published data from other centres [27, 28]. Most of our transthyretin amyloidosis patients were diagnosed during the prospective data collection period; we assume that these data are more accurate.

Since the availability of the tetramer stabilising drug Tafamidis and the RNA interference therapies Patisiran and Inotersen in Switzerland, the number of referrals of wild-type and variant transthyretin amyloidosis patients in our network has increased [15]. After a drug is approved by Swissmedic and subsequently included in the Federal Office of Public Health (FOPH) list of specialties, patients must be referred to a designated centre to apply for reimbursement [15]. With the new treatment options, awareness of the disease is increasing.

Figure 3: Overall survival in light-chain and transthyretin amyloidosis. AL: light-chain amyloidosis; ATTR: transthyretin amyloidosis.



Completeness of the dataset

In our registry, the cohort consists of a retrospective and a prospective part, with a larger proportion of missing data in the retrospective cohort. This is understandable and yet we believe it highlights the importance and impact of such registries in terms of patient outcome. Missing data might lead to incomplete staging and suboptimal treatment, given that risk adaptation is a cornerstone of the treatment of patients with systemic amyloidosis. Of our light-chain amyloidosis patient data, 75.6% of the missing staging data came from the retrospective cohort. The same applies for data on iFISH (73.2%) and plasma cell infiltration in the bone marrow (90%). These parameters must be considered when choosing the best treatment options for patient. However, our data do not allow us to reach a conclusion of worse outcome as the general number of patients in the registry is still low.

Change of practice

When founding the Collaborative Amyloidosis Network, great efforts were undertaken to standardise our diagnostic pathways and treatment recommendations. The data from our registry not only shows a more complete dataset, but also shows the implementation of change of practice, such as comprehensive testing for *TTR* mutations in transthyretin amyloidosis patients as recommended by ISA guidelines. However, and in contrast to other European countries, Swiss health insurers assess the necessity for genetic testing on a case-by-case basis. This might explain why genetic testing could only be performed in 74% of the patients. Collecting information on the mutational landscape in Switzerland is important because hereditary amyloidosis is very heterogeneous with regionally different clinical manifestations and mutation patterns. Therapy options may differ for patients with and without *TTR* mutations [29, 30].

These practice changes within the network further resulted in a national initiative, where experts from all over Switzerland drew up Guidelines for the treatment of light-chain and transthyretin amyloidosis, also published in Swiss Medical Weekly [19, 31].

Limitations

Our registry has some limitations, which are inherent to all multicentre registries. As stressed before, the retrospectively collected data are prone to be less homogeneous and less complete than the data collected prospectively from 2015 and even though we have standardised follow-up recommendations for the members of the Collaborative Amyloidosis Network, some centres might prefer local guidelines, leading to a partially incomplete dataset. Also, the absence of a central laboratory where all samples on amyloidosis would be analysed and the absence of a centralised imaging team might lead to some variability in the reporting of the results. Our cohort is still quite small, which is in part attributable to the rather strict inclusion criteria that allowed for the inclusion of only confirmed systemic amyloidosis cases, and the restriction imposed by the local ethics committee to not include patients without informed consent if they were lost to follow-up, and/or could not be tracked due to changes in address or due to death. Further, funding for medical registries is a challenge as the operating period is usually several years and direct endpoints/outcome are not always clear.

However, given the prospective character of the registry including a standardised follow-up and data collection procedure from 2015 onwards, we expect higher-quality data from this database in the future.

Conclusion

During the set-up of the registry, a more comprehensive work-up of our patients suffering mainly from light-chain and transthyretin amyloidosis was implemented. Survival rates were remarkably high and similar between light-chain and transthyretin amyloidosis, a finding which was noted in similar historic registries of international centres. However, further studies are needed to depict morbidity and mortality as the amyloidosis landscape is changing rapidly.

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