EPH255

Characteristics of Patients with ATTR Amyloidosis and Methodological Approaches for Establishing Clinical Subtype in the Netherlands

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INTRODUCTION

Challenges with ICD-10 code reliability in real world data

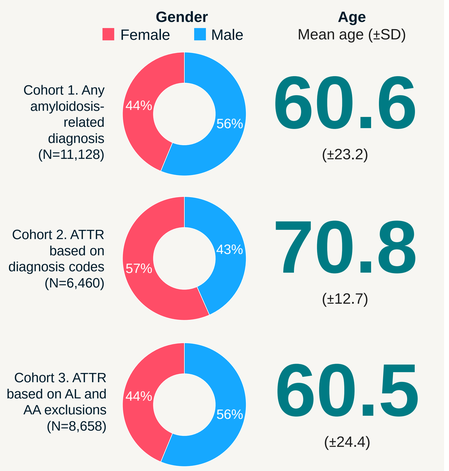
- In real world data (RWD), identification of patients with rare disease can be challenging due to the size of patient population, under- or mis-diagnosis in clinical practice, and ICD-10 code granularity.
- In transthyretin amyloidosis (ATTR), patients can present with protein deposits in the heart (ATTR-cardiomyopathy [CM]) or nerves (ATTR-peripheral neuropathy [PN]) and as hereditary (ATTRv) or wildtype (ATTRwt).[1,2]
- Diagnosing ATTR and its subtypes is complex, involving blood tests, tissue biopsy, protein analyses, scans, and genomic testing.[1,3]
- Care management occurs in multiple settings, depending on patient characteristics, disease presentation, severity, and progression.
- Lack of international consensus on ATTR, classification, coupled with limited specificity of ICD-10 codes, poses a challenge in conducting observational research on this understudied rare patient population.

OBJECTIVES

Characterize an understudied rare disease patient population

- Characterize patients with an amyloidosis-related diagnosis in hospital or ambulatory consultation setting
- Explore methods for determination of ATTR subtypes of cardiomyopathy, peripheral neuropathy, hereditary, and/or wildtype

Figure 1. Demographic characteristics



METHODS

Retrospective observational research study in the PHARMO Data Network

- The PHARMO Data Network[4] is a population-based network of electronic healthcare databases and combines anonymous data from different primary and secondary healthcare settings including general practitioners (GP), pharmacies, hospitals and clinical laboratories, with structural linkage to, amongst others, the National Pathology Registry (PALGA).
- We defined 3 cohorts for analysis between 2012-2022, with patients selected from the hospital data of the PHARMO Data Network based on hospital admissions or ambulatory consultations of amyloidosis:

  Cohort 1. Patients with any *hospital-based amyloidosis-diagnosis*: ICD-10 E85 (higher level)

  Cohort 2. Patients with ATTR relying strictly on available ICD-10 codes: E85.1, E85.2, E85.4, E85.82 (E85.8 in practice) (more granular)

  Cohort 3. Patients with suspected ATTR relying on higher level ICD-10 code (E85) and excluding patients with suspected light chain amyloidosis (AL)[5] or secondary amyloidosis (AA)[6]: Suspicion was estimated based on ICD-10 E85.81 (E85.8 in practice), E85.3, receipt of chemotherapy or stem cell transplantation, repeat visits to hematology or rheumatology specialists, and/or treatment with auto-immune medication.
- Patients were characterized in terms of demographics, comorbidities, and high-cost medicine use.

RESULTS

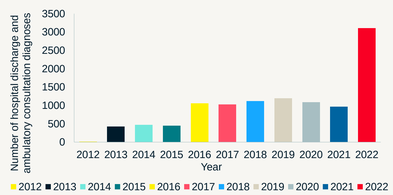
Multiple approaches for defining an ATTR cohort

- Cohort 1 yielded a sample of 11,128 patients with *any* amyloidosis-related diagnosis
- Cohort 2, approach 1 for suspected ATTR identified 6,460 patients (58% of cohort 1)
- Cohort 3, approach 2 for suspected ATTR identified 8,658 patients (78% of cohort 1)

Rising diagnosis rates in the last year

which may be due to improved diagnostic pathways, availability of recently launched amyloidosis-related treatment, and awareness of and utilization of ICD-10 codes.

Figure 2. Year of diagnosis, *any* amyloidosis-related condition (Cohort 1, N=11,128)



- The most common hospital-based comorbidities included: hypertension, atrial fibrillation, presence of cardiac and vascular implants and grafts, heart failure, chronic ischemic heart disease, lipoprotein metabolism disorder or other lipidaemia (Table 1).
- The most frequently prescribed high-cost medication classes were antineoplastic agents, selective immunosuppressants, and alkylating agents (Table 1).

Discussion

- The majority of patients with an amyloidosis-related diagnosis appear to be ATTR rather than AL or AA. Of these, identified comorbidities point to a higher incidence of the cardiomyopathy subtype. However, further research is needed to validate subtypes, with algorithm development recommended to support patient identification and classification for future studies
- Patients with complex conditions are often managed in a specialist setting, observable in ambulatory consultation. Similarly, clinical endpoints and a significant level of healthcare resource use may occur in a hospital setting due to complications and comorbidities arising from the diseases. Whilst this research in the hospital database provides good insight into the patient population, linkages across GP, clinical labs, inpatient/outpatient pharmacy, and pathology may provide richer avenues for cohort selection and outcomes evaluation. An initial feasibility assessment of the PHARMO Data Network's ability to address future research is summarized below (Table 2).

Table 1. Most occurring comorbidities and high-cost medicines in amyloidosis and ATTR cohorts

	Cohort 1. *Any* amyloidosis-related diagnosis (N=11,128)		Cohort 2. ATTR based on diagnosis codes (N=6,460)		ATTR based on AL and AA exclusions (N=8,658)	
Top 10 hospital admissions	**n**	**%**	**n**	**%**	**n**	**%**
Essential (primary) hypertension	1,769	16%	1,304	20%	1,387	16%
Personal history of certain other diseases	1,093	10%	842	13%	896	10%
Atrial fibrillation and flutter	950	9%	675	10%	708	8%
Heart failure	676	6%	436	7%	468	5%
Presence of cardiac and vascular implants and grafts	684	6%	487	8%	513	6%
Chronic ischaemic heart disease	677	6%	476	7%	505	6%
Disorders of lipoprotein metabolism & other lipidemias	652	6%	491	8%	497	6%
Type 2 diabetes	620	6%	423	7%	490	6%
Intracerebral haemorrhage	571	5%	537	8%	529	6%
Personal history of malignant neoplasm	563	5%	389	6%	427	5%
Top 10 ambulatory consultations	**n**	**%**	**n**	**%**	**n**	**%**
Medical observation, evaluation	1,077	10%	673	10%	779	9%
Heart failure	652	6%	404	6%	438	5%
Atrial fibrillation and flutter	659	6%	455	7%	486	6%
Pain in throat and chest	571	5%	356	6%	397	5%
Abdominal and pelvic pain	527	5%	176	3%	387	4%
Multiple myeloma and malignant plasma cell neoplasms	464	4%	216	3%	146	2%
Intracerebral haemorrhage	457	4%	433	7%	421	5%
Unknown and unspecified causes of morbidity	451	4%	333	5%	349	4%
Follow-up exam after treatment of non-malignant neoplasms	445	4%	299	5%	343	4%
Other malignant neoplasms of skin	395	4%	309	5%	317	4%
Top 5 drug classes, high-cost medicines database	**n**	**%**	**n**	**%**	**n**	**%**
Other antineoplastic agents	326	3%	147	2%	67	1%
Selective immunosuppressants	222	2%	89	1%	35	<0.5%
Alkylating agents	210	2%	87	1%	39	<0.5%
Monoclonal antibodies and antibody drug conjugates	157	1%	103	2%	96	1%
Vitamin K and other hemostatics	70	1%	61	1%	56	1%

Table 2. Assessment of variable availability in PHARMO Data Network using a red-amber-green qualitative assessment rating scale

Outcomes	Assessment of availability	
Demographics, patient characteristics	▪ Age, sex, geographic region available ▪ Race/ethnicity not captured	▪ Body mass index, physiological data, and family history available in GP
Amyloidosis disease characteristics	▪ TTR genetic test results available in pathology registry ▪ Clinical manifestations, comorbidities available as hospital diagnosis codes, GP record, or treatment use as proxy ▪ Left ventricular ejection fraction (LVEF) available for a subset of patients in GP	▪ Troponin T, B-type natriuretic peptide, aminoterminal pro B-type natriuretic peptide, immunoglobulins available for a subset of patients in clinical labs ▪ Staging, New York Heart Association (NYHA) severity not available
Diagnostic procedures	▪ Biopsy available in pathology registry	▪ Imaging – whether a test was performed is captured; the actual result/scan not available
Treatments	▪ Inpatient/outpatient pharmacy ▪ High cost medicines database	▪ Hospital procedures (e.g., liver transplant) ▪ Treatment offered through clinical trial
Laboratory tests	▪ Bloods and urine available for a subset of patients	
Healthcare resource use	▪ Outpatient visits, ambulatory consultation/specialty visits, outpatient occupational therapy, physiotherapist, outpatient professional carer, emergency department, hospitalization, GP	▪ Healthcare costs based on national charge rates ▪ Pharmacy costs are directly available
Clinical outcomes	▪ Mortality, cardiac transplant, liver transplant, new amyloidosis manifestation, and hospitalization available	▪ Neuropathy impairment score, nerve conduction study, 6-minute walk test not expected to be available
Quality of life	▪ Not expected to be available	

As with any secondary real world data source, observations are reflective of routine clinical care. Not all patients may have received a relevant test or diagnostic, based on the discretion of their treating physician.

KEY TAKEAWAYS

- In rare diseases, cohort identification and clinical subtyping can be a challenge.
- Awareness of amyloidosis and advancements in diagnostic technology have improved in recent years, with number of diagnoses increasing dramatically between in 2022 onward.
- Of amyloidosis-related diagnoses, ATTR appears to be the most prevalent. Of suspected ATTR diagnosis, ATTR-CM appears to occur more frequently.

CONCLUSIONS

- The PHARMO Data Network provides valuable insights into clinical subtypes of disease, particularly for rare conditions where manifestation of signs and symptoms may span multiple care settings and diagnostic modalities.
- Additional research is needed to better understand the ATTR population, including markers of disease severity, risk factors associated with hereditary vs. wild-type presentation, and burden of illness associated with different ATTR subtypes (e.g., rate of hospitalizations).

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