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Cardiac amyloidosis in a Swiss autopsy cohort – distribution and clinical relevance

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Summary

AIMS: Cardiac amyloidosis (CA) characterised by myocardial amyloid accumulation is likely underdiagnosed. The distribution and extent of myocardial amyloid deposits remain unclear. With the emergence of disease-modifying drugs for ATTR and AL amyloidoses, early detection has become increasingly important. We aim to determine the frequency, clinical relevance and distribution of amyloid subtypes in cardiac amyloidosis in an autopsy cohort.

METHODS: We retrospectively analysed consecutive unselected adult autopsies with cardiac amyloidosis over 10 years (January 2014 – December 2023). Two pathologists applied a biventricular semi-quantitative scoring system for interstitial and vascular amyloid deposits. Histopathological findings were correlated with ante mortem clinical data.

RESULTS: Cardiac amyloidosis was found in 104 of 1972 autopsies (5%) with 91% neither diagnosed nor suspected ante mortem based on documentation in digital medical records. Ninety-eight patients (94%) had amyloid transthyretin-cardiac amyloidosis (ATTR-CA) and six (6%) amyloid light chain-cardiac amyloidosis (AL-CA). AL-CA patients were younger than ATTR-CA patients (mean ± SD: 73.2 ± 15.3 vs 84.2 ± 8.1, p = 0.006) and systemic amyloidosis was more frequent (100% vs 38%, p = 0.003). Female patients (40.4%) were significantly older (mean ± SD: 85.8 ± 8.1 years) than males (82.0 ± 9.2 years, p = 0.23), and male sex was associated with clinical suspicion and diagnosis (88.9% in males vs 11.1% in females, p = 0.06). A high vascular amyloid score correlated with systemic amyloidosis (left ventricle, p = 0.003; right ventricle, p = 0.013). Right ventricular amyloid burden was strongly linked to clinical suspicion and detection (p = 0.001).

CONCLUSIONS: Our autopsy analysis found that most cardiac amyloidosis cases were undiagnosed ante mortem, especially ATTR-CA in older patients with less systemic involvement. Underdiagnosis was more pronounced in females. Our findings suggest that high vascular amyloid burden contributes to systemic amyloidosis and links right ventricular amyloid to clinical suspicion and detection.

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Introduction

Cardiac amyloidosis (CA) is a storage disease characterised by extracellular deposition of insoluble misfolded amyloidogenic proteins [1, 2]. Clinically, it is frequently identified at a late stage, particularly ATTR amyloidosis. As a progressive disorder, it carries a poor outcome if left untreated [3]. Currently, more than 40 proteins are known to be capable of aggregating as amyloid in vivo, of which nine have been detected in the heart so far [4]. The most frequent forms are amyloid transthyretin-cardiac amyloidosis (ATTR-CA) and amyloid light chain-cardiac amyloidosis (AL-CA) [5–7]. The early identification of ATTR and AL amyloidoses is of paramount importance in view of the availability of disease-modifying drugs such as tafamidis for ATTR-CA and the anti-CD38 monoclonal antibody daratumumab for AL-CA [5, 8].

ATTR-CA, predominantly acquired wild-type amyloid transthyretin (ATTRwt), is closely linked to ageing, invariably affects the heart and has a median survival of 57 months from diagnosis [9]. Conversely, hereditary forms of transthyretin amyloidosis (ATTRv) represent a less common and heterogeneous group, which frequently exhibits extracardiac manifestations, and a variable pene-

ABBREVIATIONS

AA-CA	serum amyloid A-cardiac amyloidosis
AL-CA	amyloid light chain-cardiac amyloidosis
ATTR-CA	amyloid transthyretin-cardiac amyloidosis
ATTRv	variant form of amyloid transthyretin
ATTRwt	wild-type amyloid transthyretin
CA	cardiac amyloidosis
ESC	European Society of Cardiology

trance and prognosis based on the specific mutation involved [10–13]. Studies indicate that ATTR amyloidosis is a frequently overlooked cause of increased left ventricular wall thickness (LVWT), particularly in individuals aged 65 or older, including those with hypertrophic cardiomyopathy (5%), heart failure with preserved ejection fraction (HFpEF) (13%) or severe aortic stenosis undergoing transcatheter aortic valve implantation (TAVR) (16%) [14–17].

AL amyloidosis is caused by a B cell clone producing an amyloidogenic light chain and can affect all organs except for the central nervous system. The heart is affected in up to 70% of AL amyloidosis cases [1, 18]. The overall median survival is 24 months from diagnosis, dropping to 6 months if untreated heart failure is present at diagnosis [19, 20]. Acquired AA amyloidosis is a less common form of amyloidosis caused by the overproduction and accumulation of the acute-phase protein serum amyloid A that can be highly expressed in patients with chronic inflammation, cancers or (auto)inflammatory diseases [21]. Cardiac involvement was found in 5% of cases diagnosed with AA amyloidosis and was associated with a median survival of 133 months [1, 21].

In a recent study, our research group looked at the frequency of undiagnosed diseases in autopsies and we found that up to 8% of all autopsies conducted at our institution had cardiac amyloidosis that was clinically undiagnosed prior to death in patients older than 18 years at death [22]. The true epidemiology of cardiac amyloidosis remains uncertain as not all deceased patients undergo postmortem examination [23, 24]. Various studies indicate that cardiac amyloidosis is more prevalent than previously assumed, particularly among elderly patients [23, 25–27]. In fact, postmortem investigations have reported cardiac amyloidosis in 22–25% of patients aged over 80 years [25] and in 14–32% of those aged over 75 years [26]. A single-centre study from Italy has recently reported a 43% incidence of cardiac amyloidosis (50% ATTR and 50% AL) in hearts from patients aged 75 years or over [27]. The presence of cardiac amyloidosis significantly correlated with age, hypertension, chronic kidney disease, coronary artery disease and hypertensive cardiomyopathy in our previous study [22].

While previous studies in Japanese and Italian populations have explored select clinicopathological correlations, none has specifically assessed the association between ante mortem clinical detection and the extent of interstitial or vascular amyloid deposition [27–29]. The aim of the present study was to characterise the frequency of amyloid subtypes in a Swiss autopsy cohort and to investigate the histological burden of cardiac amyloidosis in patients with a missed diagnosis during life, focusing on potential links with clinical recognition. To our knowledge, this is the first study to examine an autopsy-confirmed cardiac amyloidosis cohort in Switzerland, offering new insights into diagnostic gaps and their pathological correlates.

Materials and methods

Patient cohort

We conducted a retrospective review of 1972 reports of unselected consecutive whole-body autopsies of adults performed at the Department of Pathology and Molecular Pathology of the University Hospital of Zurich, Switzerland, between 1 January 2014 and 31 December 2023. Autopsy reports were screened to identify patients with cardiac amyloidosis. Each autopsy had been performed by a pathology resident under the supervision of a board-certified pathologist according to a standardised protocol as previously described [22, 30]. This protocol also includes the heart autopsy and the routine histological analysis of four samples of myocardial tissue from various anatomical regions (anterior and posterior cardiac wall, septum and right ventricle). Presence of amyloidosis was identified on routine Haematoxylin & Eosin and Elastin-van Gieson staining and verified by Congo Red staining. On Haematoxylin & Eosin staining, it appears as an amorphous eosinophilic substance within the interstitium and stained with Congo Red shows a yellow-green birefringence under polarised light [31]. All cases with evidence of cardiac amyloidosis underwent additional staining with a standard immunohistochemical panel (ATTR, AL and AA) to classify the type of amyloidosis, following the recommendations of Linke [32].

Consent for the autopsy (either by the relatives or in a few cases by the deceased patient's will) was obtained for all cases. The study was conducted in compliance with Swiss federal research regulations and received approval from the institutional review board and Cantonal Ethics Committee Zurich (Identifier BASEC-Nr. 2024-01760).

Immunohistochemistry

Amyloid immunohistochemistry was performed using amYmed (ATTR, AL) and Dako (AA) antibodies (see appendix table S1). Signal amplification and visualisation were done with the OptiView DAB IHC Detection Kit (Ventana Medical Systems) for ATTR and AL and with the IHC Refine Kit (Biosystems) for AA, following the manufacturers' protocol. Slides were counterstained with haematoxylin, sequentially dehydrated and coverslipped for microscopic evaluation. AL was only considered detected if both antibodies (HAR and ULI/LAT) appeared positive.

Amyloid scores and clinical data

Clinical data were obtained from referral documents for autopsies and electronic medical records. Patients were classified as having been diagnosed or suspected of cardiac amyloidosis ante mortem based on the available clinical information. For patients who died at our institution, full electronic medical records – including cardiology notes and imaging reports – were reviewed. In patients for whom no electronic medical records were available (i.e. externally referred cases), classification was based solely on the referral documents submitted for autopsy. The classification terminology reflects the wording used in the original clinical documentation: patients in whom amyloidosis was discussed as a differential diagnosis or was under investigation and explicitly phrased as "suspected" were categorised as suspected, while those in whom the diagnosis was documented as established were categorised as diagnosed. This approach was chosen to reflect how patients were clinically classified ante mortem.

Patients with available cardiological documentation within one year prior to death were included in a subgroup analysis of clinical manifestations.

Descriptive statistics were used to analyse the frequency of cardiac amyloidosis. The prevalence of cardiac amyloidosis was calculated as the proportion of cases with amyloid deposits. The causes of death were determined from the autopsy reports. The categories were based on their primary affected system or pathological process in relation to the clinical context. Cases in which the amyloidosis was directly related to the cause of death were additionally noted.

We developed a semi-quantitative scoring system to assess the extent of amyloidosis in the myocardial tissue of the left and right ventricles, as well as in the myocardial vessels of the left and right ventricles. On Haematoxylin & Eosin and immunohistochemistry slides, the percentage of amyloid deposition was quantified in relation to the surface area of the tissue sample resulting in myocardial scores from 1 to 10 (table 1). The affected vessels were quantified in relation to the total number of vessels present on the sample, resulting in vessel scores from 1 to 4 (table 1).

Two experienced pathologists (AB and UM) independently evaluated the histology of myocardial tissue from cases with cardiac amyloidosis. The myocardial and vascular scores of the left and right ventricles were assessed for each case, both on Haematoxylin & Eosin and on immunohistochemistry. In the event of any discrepancies, a joint evaluation was conducted in order to reach a consensus on the score.

Statistical analyses were performed using SPSS version 29.0.1.1 (IBM Corp, Armonk, New York, USA). The extent of amyloidosis was correlated with demographic variables (age and sex) and with other clinicopathological variables (presence of systemic vs cardiac-only amyloidosis, amyloidosis type) using Kendall's tau-b test. The closer the correlation coefficient (τb) is to 1 or −1, the stronger the correlation between the variables is assumed to be [33].

Binary variables were compared with each other using Fisher's exact test. Given the exploratory nature of these analyses, no adjustment for multiple testing was performed. Assessment for statistical significance in the subgroup analysis for clinical data was evaluated using the independent T-test for normally distributed values and the Mann-Whitney U test for non-normally distributed values. Results were considered statistically significant when the p-value was less than 0.05. Figures were created using GraphPad Prism 10.3.1.

Table 1:
Scoring system to evaluate the extension of amyloidosis in myocardial tissues and in myocardial vessels.

Score	Extent of amyloidosis
	Percentage of myocardium containing amyloid
0	0%
1	1–10%
2	11–20%
3	21–30%
4	31–40%
5	41–50%
6	51–60%
7	61–70%
8	71–80%
9	81–90%
10	91–100%
	Percentage of myocardial vessels containing amyloid
0	0%
1	1–10%
2	10–50%
3	50–90%
4	90–100%
5–10	Not applicable

Results

Clinicopathological correlation

Cardiac amyloidosis was identified in 104 of 1972 autopsies (5.3%). Among these cases, the diagnosis was made at the time of autopsy in 95 of 104 patients (91.3%), while in six patients (5.8%) cardiac amyloidosis had been diagnosed prior to death. Cardiac amyloidosis was suspected prior to death but confirmed only at autopsy in 4 patients (2.9%). Females were slightly older, with a mean ± SD age of 85.8 ± 8.1 years vs 82.0 ± 9.2 years in males.

Table 2 details the types and distribution of cardiac and systemic amyloidoses among the patients. Ninety-eight patients (94.2%) were diagnosed with ATTR amyloidosis, while only 6 (5.8%) had AL amyloidosis. There was no AA amyloidosis. The majority of patients in both subgroups were male (59.2% in ATTR-CA and 66.7% in AL-CA). Among patients with AL-CA, 66.7% (4/6 patients) received an ante mortem diagnosis, with no cases classified as suspected, whereas 5.1% (5/98 patients) of ATTR-CA patients were clinically identified (2 diagnosed, 3 suspected). Relevant imaging findings, including echocardiography and, in two cases, cardiac magnetic resonance imaging (CMR), that contributed to the clinical suspicion or diagnosis are summarised in appendix table S2. One patient had cardiac amyloidosis confirmed histologically through myocardial biopsy performed during emergency surgery. None of the patients underwent 99mTc-DPD scintigraphy. In three patients, classification as diagnosed vs suspected vs undiagnosed was based solely on the referral documents provided with the autopsy request.

Notably, AL-CA cases demonstrated a significantly stronger association with clinical suspicion or diagnosis compared to ATTR-CA (τb = 0.489, p <0.001, n = 104). A statistically significant correlation was observed between patient age at death and amyloidosis type: patients with AL-CA (mean ± SD age: 73.2 ± 15.3 years) were found to be significantly younger than those with ATTR-CA (84.2 ± 8.1 years), as illustrated in figure 1A.

Sixty of 104 patients (57.7%) exhibited solely cardiac amyloidosis, while 44 cases (42.3%) presented with systemic amyloidosis (see table 2), which is defined as amyloidosis involving multiple organ systems [31]. Patients with AL-CA were found to have a higher prevalence of systemic amyloidosis than ATTR-CA patients: 100% in AL (n = 6) vs 38.8% in ATTR (n = 38).

The analysis of clinical information obtained prior to death revealed that the majority of patients had arterial hypertension (86.2%) and coronary heart disease (54.6%), while the "red flag" of hypotension or normotension in previously hypertensive patients was present in 23.6%. The diagnosis of heart failure with a left ventricular ejection frac-

tion (LVEF) below 50% was made in 43.6% of patients and 21.7% of patients were diagnosed with "hypertensive cardiomyopathy" or heart failure with preserved ejection fraction. Chronic kidney disease was found in 49.1%, atrial fibrillation was present in 45.5%, AV conduction disease found in 27.3% and aortic valve stenosis in 29.1%. No statistically significant differences in cardiac manifestations could be detected between ATTR-CA and AL-CA (see table 3). Among the non-cardiac findings (see appendix table S3), macroglossia ($p < 0.001$), monoclonal gammopathy of undetermined significance (MGUS) ($p < 0.001$) and haemorrhagic strokes ($p = 0.02$) were significantly more frequent in AL-CA than in ATTR-CA. Interestingly, the red flags lumbar spinal stenosis and bilateral carpal tunnel syndrome were only rarely found (7.3% and 3.6%, respectively).

Correlation to semi-quantitative amyloidosis scores

Myocardial samples of the left ventricle were available in all 104 patients and of the right ventricle in 99 patients.At autopsy, 41 patients exhibited interstitial myocardial-only amyloidosis (39.4%), whereas 22 patients had vascular-only amyloidosis (21.2%) and the remaining 41 patients had combined vascular and interstitial myocardial amyloidosis (39.4%) (see table 2 and figure 1B). Figure 2 depicts the distribution of cases based on the extent of interstitial amyloid deposition in the myocardial tissue and the extent of the vascular amyloid deposition. Figure 3 presents examples of varying degrees of interstitial and vascular amyloid deposition.

A significant correlation was identified between the vascular score and the presence of systemic amyloidosis in both the left and right ventricles (left: $\tau b = 0.261$, $p = 0.003$, $n = 104$; right: $\tau b = 0.229$, $p = 0.013$, $n = 99$). However, when focusing specifically on ATTR-CA, this relationship was evident only in the left ventricle ($\tau b = 0.248$, $p = 0.007$, $n = 94$), whereas no significant association was observed in the right ventricle ($\tau b = 0.177$, $p = 0.06$, $n = 94$).

Additionally, clinically confirmed or suspected cardiac amyloidosis was significantly associated with an increased interstitial myocardial score in both the left ($\tau b = 0.239$, $p = 0.005$, $n = 104$) and right ($\tau b = 0.28$, $p = 0.001$, $n = 99$) ventricles. Furthermore, a significant association was found between clinically known or suspected cardiac amyloidosis and the vascular score of the right ventricle ($\tau b = 0.181$, $p = 0.048$, $n = 99$), though no such relationship was detected in the left ventricle ($\tau b = 0.149$, $p = 0.09$, $n = 104$).

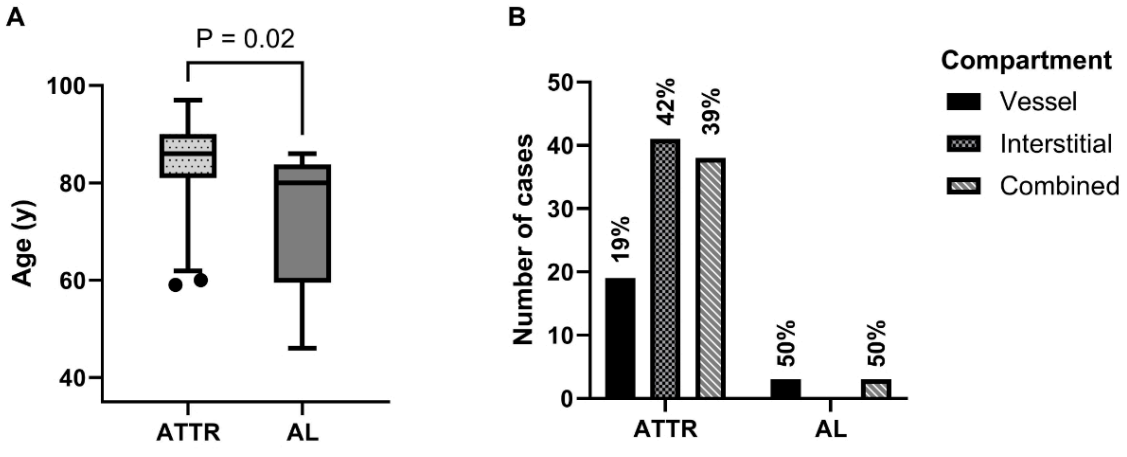
We did not find any direct correlation between myocardial fibrosis (either patchy fibrosis or isolated scars) and the vessel scores of the left ($\tau b = 0.061$, $p = 0.5$, $n = 104$) or right ($\tau b = -0.038$, $p = 0.66$, $n = 104$) ventricle. However, in the subgroup analysis, considering only patients without stenotic coronary sclerosis (defined here as no coronary artery showing >50% lumen constriction, as defined in a previous study from our group [34]), we observed a significant correlation between myocardial fibrosis and vessel scores in the right ventricle ($\tau b = 0.333$, $p = 0.04$, $n = 34$; left ventricle: $\tau b = 0.295$, $p = 0.06$, $n = 35$).

Table 2:
Types and distribution of amyloidosis in patients with cardiac amyloidosis (n = 104).

Variable		n (%)
Amyloidosis distribution	Only cardiac	60 (57.7%)
	Systemic	44 (42.3%)
Amyloidosis type	ATTR-CA	98 (94.2%)
	AL-CA	6 (5.8%)
Cardiac amyloidosis distribution	Myocardial only	41 (39.4%)
	Vascular only	22 (21.1%)
	Combined	41 (39.4%)

AL-CA: amyloid light chain-cardiac amyloidosis; ATTR-CA: amyloid transthyretin-cardiac amyloidosis.

Figure 1: (A): Age distribution of cases classified according to amyloidosis type; whiskers at 2.5 and 97.5 percentiles (p-value calculated with Mann-Whitney U test). (B): Cases classified according to the type and distribution of myocardial amyloid deposits. Percentages of cases by type. AL: amyloid light chain-cardiac amyloidosis; ATTR: amyloid transthyretin-cardiac amyloidosis.



Correlation to cause of death

The main cause of death was cardiovascular (50%, n = 52) followed by infectious and inflammatory causes (25%, see appendix table S4). Cardiac amyloidosis was directly involved in the cause of death in 29 patients (27.9%). Direct cardiac amyloidosis involvement in cause of death correlated with the interstitial myocardial scores of both ventricles (left: $\tau b = 0.392$, $p < 0.001$, n = 104; right: $\tau b = 0.334$, $p < 0.001$, n = 99) but not the vascular scores.

No correlation was found between the sex of the patient (all n = 104) and amyloidosis type ($\tau b = 0.036$, $p = 0.72$), amyloid distribution ($\tau b = -0.088$, $p = 0.37$), affected compartment ($\tau b = 0.108$, $p = 0.25$), clinical diagnosis ($\tau b = 0.184$, $p = 0.06$) or cause of death ($\tau b = 0.014$, $p = 0.88$).

Discussion

This autopsy study was designed to determine the prevalence and morphological characteristics of cardiac amyloidosis. Our findings revealed a prevalence of 5.3% for cardiac amyloidosis in a cohort of 1992 autopsies, with 94.2% of cases classified as amyloid transthyretin-cardiac amyloidosis (ATTR-CA) and the remaining 5.8% as amyloid light chain-cardiac amyloidosis (AL-CA). Patients diagnosed with AL-CA were significantly younger and more frequently exhibited systemic amyloidosis compared to those with ATTR-CA. Notably, we did not identify any cases of serum amyloid A-cardiac amyloidosis (AA-CA) in our cohort. This contrasts with a recent study from Japan, which reported a high prevalence of ATTR-CA (54.2%) alongside a substantial prevalence of AA-CA (24.4%), while AL-CA accounted for 6.1% of cases, with the remaining cases being classified as equivocal [28]. These variations may suggest geographical differences in the prevalence of cardiac amyloidosis subtypes. In fact, extensive research from Europe and the USA indicates that ATTR and AL are the predominant forms of cardiac amyloidosis, whereas cardiac involvement in AA amyloidosis is exceedingly rare [1, 2, 24, 35, 36]. Conversely, in AA amyloidosis, the kidneys are the most frequently and severely affected organ [37].

Our data highlight that 94% of cardiac amyloidosis cases were diagnosed only at autopsy, reinforcing the notion that cardiac amyloidosis remains a clinically underdiagnosed condition in clinical practice [38, 39]. ATTR-CA, in particular, is more prone to clinical underdiagnosis, likely due to its higher prevalence in elderly patients [1, 38]. Clinicians may have greater awareness of AL-CA, given its recognised association with multiple myeloma and monoclonal gammopathy of undetermined significance [1]. Notably, even though there was no significant correlation between sex and diagnosis status, in our cohort most patients with ante mortem diagnosis or clinical suspicion of cardiac amyloidosis were male (8 male, i.e. 12.9% of all males vs 1 female, i.e. 2.4% of all females). This sex disparity may further highlight the diagnostic gap and the necessity for increased clinical vigilance, especially in female patients.

The routine sampling of heart tissue of the left and right ventricle at autopsy enabled us to perform a detailed analysis of the cardiac amyloid distribution. We developed a semi-quantitative scoring system to correlate amyloid deposits with clinical findings, revealing that the clinical

Table 3:
Patient characteristics and cardiological findings.

Criteria		ATTR-CA	AL-CA	All	p-value
Total number of patients, n (%)		98 (94.2%)	6 (5.8%)	104 (100%)	
Sex, n (%)	Male	58 (59.2%)	4 (66.7%)	62 (59.6%)	
	Female	40 (40.8%)	2 (33.3%)	42 (40.4%)	
Cardiovascular risk factors, n (%)	Information available	83 (84.7%)	4 (66.7%)	87 (83.7%)	
	Arterial hypertension	73 (88.0%)	2 (50%)	75 (86.2%)	0.06
	Tobacco	23 (27.7%)	1 (25%)	24 (27.6%)	0.90
	Adiposity	21 (25.3%)	2 (50%)	23 (26.4%)	0.30
	Dyslipidaemia	22 (26.5%)	0 (0%)	22 (25.3%)	0.95
	Type 2 diabetes mellitus	15 (18.1%)	1 (25%)	16 (18.4%)	0.73
	Family history for cardiovascular disease	6 (7.2%)	0 (0%)	6 (6.9%)	0.06
Cardiological findings/diagnosis prior to death as stated in the reports, n (%)	Information available	51 (52.0%)	4 (66.7%)	55 (52.9%)	
	Hypotensive or normotensive (previously hypertensive)	11 (21.6%)	2 (50%)	13 (23.6%)	0.20
	Hypertrophic cardiomyopathy	4 (7.8%)	0 (0%)	4 (7.3%)	0.56
	Hypertensive cardiomyopathy / heart failure with preserved ejection fraction	20 (39.2%)	2 (50%)	22 (40.0%)	0.67
	Heart failure with mildly reduced ejection fraction	10 (23.3%)	0 (0%)	10 (21.7%)	0.33
	Heart failure with reduced ejection fraction	12 (27.9%)	2 (50%)	14 (30.4%)	0.25
	Coronary artery disease	28 (54.9%)	2 (50%)	30 (54.6%)	0.85
	Aortic valve stenosis	16 (31.4%)	0 (0%)	16 (29.1%)	0.19
	Aortic valve prosthesis (transcatheter aortic valve replacement or surgical replacement)	11 (21.6%)	0 (0%)	11 (20%)	0.30
	Atrial fibrillation	23 (45.1%)	2 (50%)	25 (45.5%)	0.85
	Atrioventricular conduction disease	14 (27.5%)	1 (25%)	15 (27.3%)	0.92
	Pacemaker placement	11 (21.6%)	2 (50%)	13 (23.6%)	0.20
	Implantable cardioverter-defibrillator or cardiac resynchronisation therapy	2 (3.9%)	0 (0%)	2 (3.6%)	0.69

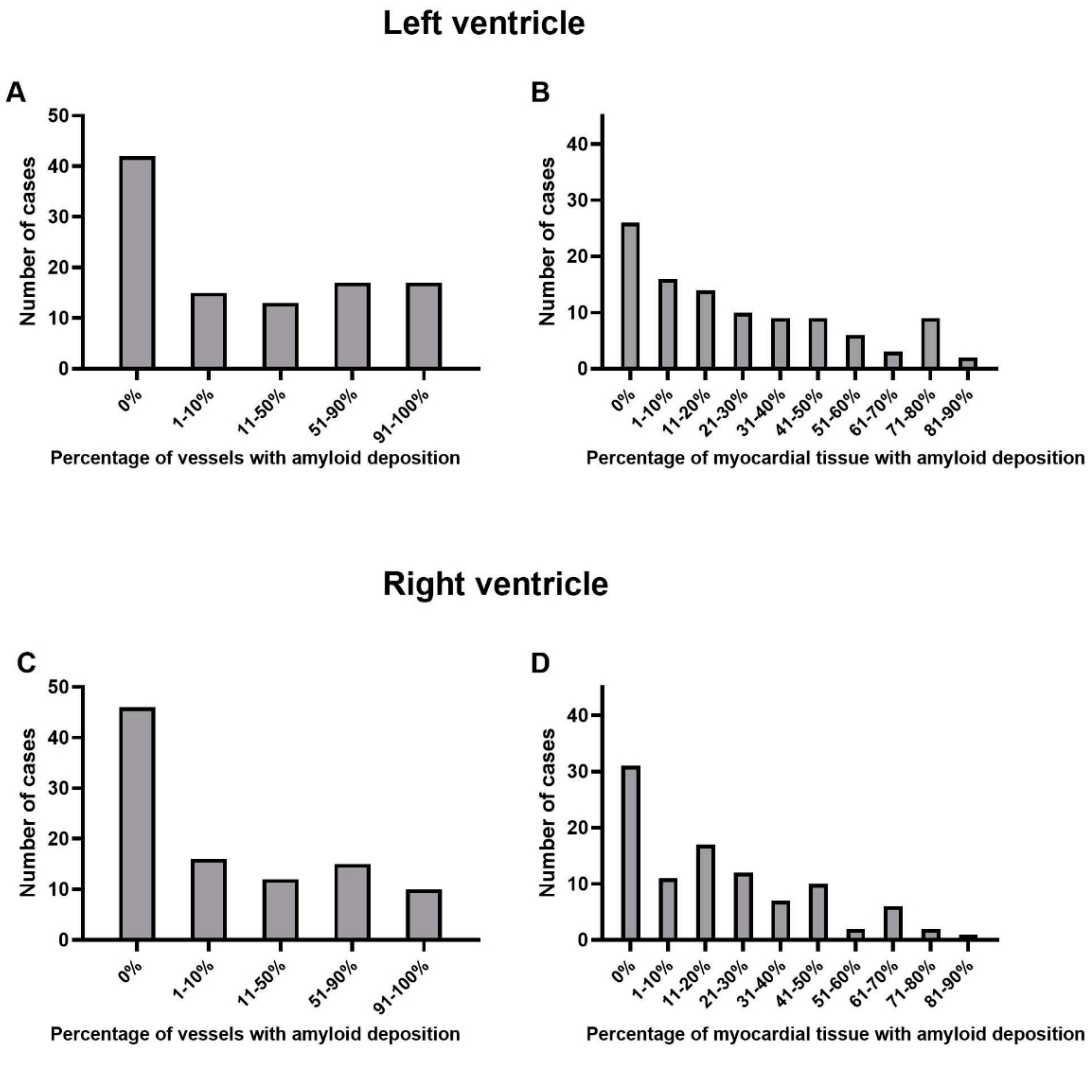
AL-CA: amyloid light chain-cardiac amyloidosis; ATTR-CA: amyloid transthyretin-cardiac amyloidosis.

likelihood of amyloid detection prior to death was significantly associated with interstitial and vascular amyloid burden in the right ventricle. In contrast, there was only a weak correlation with left ventricular interstitial amyloid and no correlation with left ventricular vascular amyloid. Our findings are in line with current research in the field of multimodality cardiac imaging that underscores the diagnostic and prognostic significance of right ventricular involvement in cardiac amyloidosis. Most recently, Datar et al. demonstrated that 18F-florbetapir PET/CT can detect early right ventricular amyloid deposition, correlating with dysfunction and major adverse cardiac events [40]. Similarly, echocardiographic right ventricular strain [41, 42] and CMR-derived right ventricular strain [43] provides a valuable diagnostic marker for cardiac amyloidosis.

While the European Society of Cardiology (ESC) guidelines on cardiomyopathies recommend screening for cardiac amyloidosis in patients with a left ventricular wall thickness of ≥12 mm [3] and at least one additional red flag, our results suggest a higher sensitivity of right ventricular alterations in predicting cardiac amyloidosis. However, it should be acknowledged that right ventricular assessment is inherently more challenging in echocardiography compared to left ventricular assessment and that the left ventricular wall thickness threshold of ≥12mm was chosen to increase the sensitivity for detecting cardiac amyloidosis, compared to the higher threshold of ≥14 mm used in other guidelines such as those from the AHA [44]. Nevertheless, it does not imply that the right ventricle is less affected or that there are no cases of cardiac amyloidosis with a left ventricular wall thickness of <12mm [45]. Given the growing recognition of right ventricular amyloid burden in cardiac amyloidosis, our study adds to the expanding body of evidence highlighting its diagnostic and prognostic value.

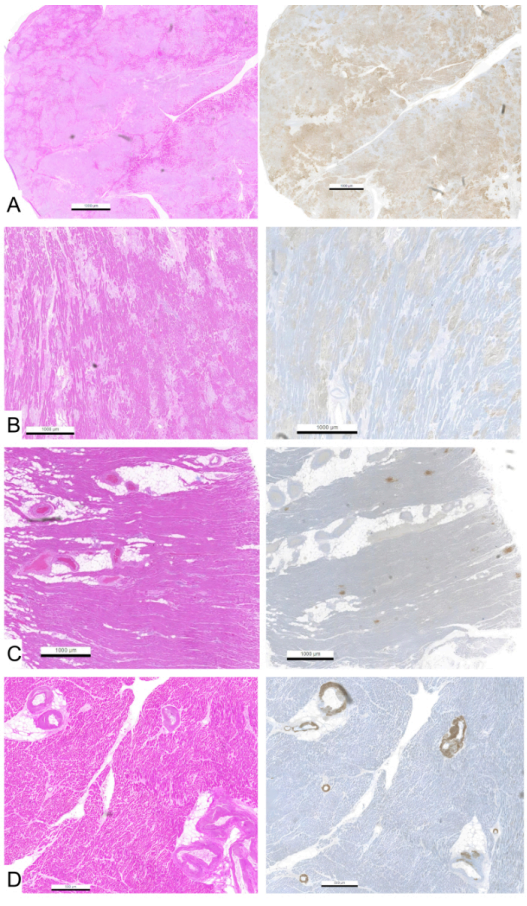
Notably, a high vascular amyloid score in both the left and right ventricles was significantly associated with systemic amyloidosis. This finding may suggest that detecting vascular amyloid in a heart biopsy could warrant further screening for systemic amyloidosis. However, in the clinical setting, the distinction between vascular and interstitial amyloid deposition is not emphasised at the moment, which represents an important novel aspect of our study. Given that vascular amyloid deposition may contribute to

Figure 2: Distribution of cases depending on the location and extent of amyloid depositions. (A and C): Percentage of myocardial vessels with amyloid deposition categorised by vascular score in the left (A) and right (C) ventricle. (B and D): Percentage of interstitial amyloid deposition in relation to the myocardial tissue surface categorised by myocardial interstitial score in the left (B) and right (D) ventricle.



systemic dysfunction, it is notable that profound vascular dysfunction was recently demonstrated in patients with amyloidosis, including at the retinal level, which could be a consequence of vascular amyloid accumulation [46]. Moreover, since systemic amyloidosis is generally presumed and actively investigated – with approximately 95% of ATTR-CA cases diagnosed via non-biopsy methods such as technetium scintigraphy – and endomyocardial biopsy is now rarely performed, these results should be interpreted with caution, particularly given the limited number of cases with systemic amyloidosis (n = 6). Larger studies are necessary to determine whether vascular amyloid detection in biopsy specimens holds additional diagnostic value for systemic amyloidosis. Interestingly, another finding was the significant association between myocardial fibrosis and vascular amyloidosis in the right ventricle, which, to the best of our knowledge, has not been previously reported in the literature. However, this result is based on a small subgroup analysis that included only patients without significant coronary stenosis. The size of this group is too limited to allow for definitive interpretations or further statistical analyses, and the observed association may be incidental or influenced by biases inherent to an autopsy-based cohort. In this context, larger studies are needed to further investigate and clarify this phenomenon.

Figure 3: Haematoxylin & Eosin slides showing different percentages of interstitial (A–C) and vascular (D) amyloid deposits with respective score and corresponding ATTR immunohistochemistry. (A): Extensive interstitial amyloid deposits in >90% of the myocardial surface, resulting in a myocardial score of 9. (B): Interstitial amyloid deposits in 50–60% of the myocardial surface, resulting in a myocardial score of 5. (C): Interstitial amyloid deposits in under 10% of the myocardial surface, resulting in a myocardial score of 1. (D): Amyloid deposits shown in >90% of myocardial vessels, resulting in a vessel score of 4.



The current ESC Guidelines for the management of cardiomyopathies recommend red flags to prompt amyloidosis screening [3]. This includes clinical, echocardiography, ECG, CMR and other categories for initiating early amyloidosis screening. In our study, most patients were diagnosed ante mortem with hypertensive heart disease (40%), heart failure with a left ventricular ejection fraction (LVEF) below 50%, and atrial fibrillation (45.5%). Additionally, common findings in our patient cohort included aortic valve stenosis (29.1%) and AV conduction disease (27.3%). However, no statistically significant differences were observed between ATTR-CA and AL-CA in ante mortem cardiological findings. It is important to note that the number of AL-CA patients in our study was limited (n=6), which may restrict the ability to detect significant differences in ante mortem findings. In contrast, extracardiac findings demonstrated clearer distinctions between the two subtypes. Macroglossia ($p = 0.0004$), monoclonal gammopathy of undetermined significance ($p = 0.0004$) and haemorrhagic strokes ($p = 0.02$) were significantly more frequent in AL-CA than in ATTR-CA, aligning with findings from multiple studies in the literature [1–4, 47]. Notably, macroglossia is a well-recognised feature exclusive to AL-CA and is not observed in ATTR-CA, further reinforcing its diagnostic significance in distinguishing between the two subtypes.

Furthermore, consistent with prior research [48], patients with AL-CA in our cohort were significantly younger and more frequently exhibited systemic amyloidosis than those with ATTR-CA did. These findings highlight key clinical distinctions between the two subtypes, emphasising the importance of extracardiac manifestations in differentiating AL-CA from ATTR-CA and underscoring the need for comprehensive diagnostic evaluation.

Further studies are necessary to assess the clinical relevance of our findings, particularly for cardiac imaging. It remains unclear how many cases of undiagnosed cardiac amyloidosis could have been detected prior to death in a clinical setting using current European guideline-based screening criteria [3]. Additionally, the significance of small amyloid deposits on symptomatology and life expectancy is uncertain. The process of ageing is associated with alterations in protein homeostasis, which in turn leads to an increased prevalence of protein misfolding [49–51]. This complicates determining whether the mere presence of amyloid deposits, particularly in instances with a low amyloid burden, has the potential to significantly affect cardiac health. However, sporadic ATTR-CA has been previously linked to an increased risk of sudden cardiac death even in the early disease stages [52]. Similarly, a recent study on forensic autopsies from Australia over a 20-year period (2003–2022) revealed that cardiac amyloidosis was a contributing factor in 11 deaths, with three being the primary cause of death [53]. Likewise, AL-CA has been implicated in sudden cardiac death [54].

Our study has limitations inherent to retrospective, single-centre autopsy research, including selection bias and a declining autopsy rate [55]. Despite routine sampling of three left myocardial regions (anterior wall, posterior wall and

septum) and one right myocardial region in each patient, this approach may not fully represent cardiac amyloidosis distribution of the entire heart. The absence of sinoatrial node and conduction tissue sampling prevents conclusions regarding conduction system involvement. Limited clinical data for some patients also constrained the analysis. Additionally, most cases were diagnosed postmortem, precluding genetic testing for hereditary ATTR amyloidosis.

Finally, it is important to consider the autopsy rate of our institution, which can be calculated as the ratio of adult autopsies to total adult deaths during the study period, yielding a value of 12.6%. This relatively low rate indicates that the cases included in the study represent only a small and specific subset of the overall population – primarily hospitalised patients, often with multiple comorbidities. It is also worth noting that the selection criteria for determining which deceased patients undergo autopsy are not clearly defined. Decisions are made on a case-by-case basis, primarily relying on individual clinical judgement and the request of the attending physician. Typically, autopsies are performed in cases of unexplained or unexpected death, complex clinical scenarios or uncertain diagnoses requiring postmortem confirmation. Consequently, these factors introduce a potential selection bias, limiting the generalisability of the findings to the broader population. In this regard, another potential source of bias is the absence of a control or survivor group, which limits the ability to draw definitive conclusions about risk factors for cardiac amyloidosis and may render such discussions largely speculative.

An additional point to consider is that our study spans a 10-year period (2014–2023) during which clinical awareness and the incentive to diagnose cardiac amyloidosis have substantially increased due to the recent availability and reimbursement of disease-modifying therapies. Therefore, our findings may underestimate current diagnostic rates and reflect clinical practices that have evolved over the course of the study period.

In conclusion, our study provides valuable epidemiological insights into cardiac amyloidosis, highlighting its underdiagnosis. Further investigation is necessary to determine the clinical implications of our findings and their impact on patient management.

Data sharing statement

The data underlying this study are of a sensitive nature and therefore will not be made publicly available on open data repositories. However, deidentified data may be made available upon reasonable request, subject to approval by the corresponding author and the Director of the Department of Autopsy of our institution.

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Appendix

Table S1. Amyloid staining antibodies

Amyloid antibody	Dilution	Manufacturer	Oder No	Kit
ATTR (polyclonal)	1:5	amYmed	Y180	Optiview DAB
AL lambda (HAR) (polyclonal)	1:5	amYmed	Y120	Optiview DAB
AL lambda (ULI/LAT) (polyclonal)	1:5	amYmed	Y130+1	Optiview DAB
AA (monoclonal)	1:1000	DAKO A/S	M0759	IHC Refine

Table S2. Patients with antemortem suspicion or diagnosis of CA

Patient	Sex, age, CA type	Echocardiography (time before death)	Clinical Report	CMR, Scintigraphy or Biopsy (time before death)
Suspected				
#1	Male, 76 years, ATTR	CA discussed as differential diagnosis due to biventricular hypertrophy, no strain available (16.8 months)	Cardiomyopathy of unknown origin at death, echo suspicious for CA, but fat biopsy negative, no other tests available	n/a
#7	Male, 90 years, ATTR	n/a	Clinical suspicion mentioned on referral report for autopsy, no other information available	n/a
#8	Male, 83 years, ATTR	High CA Suspicion: biventricular hypertrophy and apical sparing (23 months)	Hypertrophic Cardiomyopathy, CA suspicion during hospitalization for TAVR, Immunofixation negative	Scintigraphy was planned, but didn't take place
Diagnosed				
#3	Male, 71 years, AL	CA Suspicion (9 days): LV hypertrophy, granular sparkling appearance of the myocardium	Diagnosed as HCM 9 years before. Spontaneous VSD Diagnosis during CMR for HCM with simultaneous CA Diagnosis. Perioperative Death.	Myocardial biopsy during surgery showed severe CA deposits (12 days), CMR with typical LGE (6 days)
#6	Male, 88 years, ATTR	CA Suspicion (13 months): LV hypertrophy, granular sparkling appearance of the myocardium, apical sparing	Diagnosis based on echocardiography during follow-Up 8 months after TAVR	n/a
#2	Female, 86 years, AL	n/a	Diagnosis on referral report for autopsy, no other info available	n/a
#4	Male, 46 years, AL	CA Suspicion (2 months): LV hypertrophy, apical sparing	Diagnosis of CA made during diagnosis of Morbus Waldenström (2 months before death), ICD implantation 2 month before death for ventricular arrhythmia	CMR with typical LGE (7 weeks)
#5	Male, 64 years, AL	CA Suspicion (19 months): LV hypertrophy, granular sparkling appearance of the myocardium, apical sparing	CA Diagnosis 2 months after diagnosis of lymphoplasma-cytic lymphoma with IgG paraprotein, pacemaker placement for AV-block (17 months before death)	n/a

Table S3. Non-cardiac antemortem clinical findings

Criteria	ATTR N (%)	AL N (%)	All N (%)	p-value
Information available	51 (52.0)	4 (66.7)	55 (52.9)	
Angiology				
Aortic disease	10 (19.6)	0 (0)	10 (18.2)	0.33
Peripheral arterial disease	9 (17.7)	1 (25)	10 (18.2)	0.87
Pulmonology				
Chronic obstructive pulmonary disorder	4 (7.3)	1 (25)	4 (7.3)	0.16
Nephrology				
Chronic kidney disease	24 (47.1)	3 (75)	27 (49.1)	0.29
Dialysis	6 (11.8)	0 (0)	6 (10.9)	0.47
Neurology				
Ischemic stroke	9 (17.7)	1 (25)	10 (18.2)	0.72
Hemorrhagic stroke	1 (2.0)	1 (25)	2 (3.6)	**0.02**
Unexplained polyneuropathy	4 (7.8)	0 (0)	4 (7.3)	0.56
Hematology				
MGUS	0 (0)	2 (50)	2 (3.6)	**<0.001**
Gastroenterology				
Liver cirrhosis	2 (3.6)	0 (0)	2 (3.9)	0.69
Unexplained gastrointestinal symptoms	4 (7.8)	0 (0)	4 (7.3)	0.78
Musculoskeletal				
Lumbar spinal stenosis	4 (7.8)	0 (0)	4 (7.3)	0.56
Bilateral carpal tunnel syndrome	2 (3.9)	0 (0)	2 (3.6)	0.19
Bilateral hip arthroplasty	2 (3.9)	0 (0)	2 (3.6)	0.69
Others				
Macroglossia	0 (0)	1 (25)	1 (1.8)	**<0.001**
Deafness	4 (7.8)	2 (50)	6 (11.8)	0.56

Table S4. The causes of death (categories) in 104 patients

Category	Diagnoses
Cardiovascular (N=52)	• Myocardial infarction • Heart failure • Cardiogenic shock • Ruptured Aneurism
Respiratory (N=7)	• Respiratory failure • Pulmonary embolism
Infectious/ Inflammatory (N=26)	• Pneumonia • Myocarditis • Pancreatitis • Sepsis
Central Nervous System (N=6)	• Stroke • Hypoxic-ischemic encephalopathy • Intracerebral hemorrhage
Other (N=13)	• Malignancies • Multi-organ failure • Cardiorespiratory insufficiencies • Hemorrhagic shock caused by gastrointestinal bleeding • Liver failure