



Role of autopsy in sudden deaths from undiagnosed cardiac amyloidosis: a systematic review with an illustrative autopsy case

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ABSTRACT

Background/Introduction: Cardiac amyloidosis (CA) is an infiltrative cardiomyopathy that remains under-diagnosed and may be overlooked in sudden-death investigations. We reviewed the contribution of autopsy and post-mortem methods to recognizing CA and clarifying fatal mechanisms.

Methods: We searched PubMed/MEDLINE from database inception through 10 July 2026 using a predefined Boolean query and supplementary reference-list screening. Nineteen eligible reports were included and narratively synthesized across epidemiology, terminal mechanisms, and post-mortem diagnostic techniques.

Results: Autopsy studies documented frequent ante-mortem underdiagnosis: prevalence reached 21% in unselected elderly populations, and 91.3% of cases in a cohort of 1972 autopsies had been missed during life. Sudden death was especially relevant in AL amyloidosis and commonly involved pulseless electrical activity (PEA), bradyarrhythmias, or conduction disease. In the EXCALIBUR study of 110 newly diagnosed patients, bradyarrhythmias requiring pacemaker implantation occurred in 17.3% and new-onset atrial fibrillation in 28.2%; terminal rhythms were predominantly PEA. A previously reported illustrative autopsy case of systemic AL kappa amyloidosis showed how multisystem symptoms, low-voltage ECG, renal dysfunction, and a monoclonal kappa component may remain clinically unintegrated.

Conclusions: Targeted autopsy, mapped histological sampling, Congo red staining, and reliable amyloid typing can identify otherwise unrecognized CA, improve cause-of-death attribution, and resolve medicolegal uncertainty. Correlating ante-mortem warning signs with post-mortem findings may reduce diagnostic misclassification.

1. Introduction

Cardiac amyloidosis (CA) is a progressive infiltrative cardiomyopathy characterized by the extracellular deposition of insoluble misfolded protein fibrils within the myocardium, leading to the disruption of tissue architecture and severe functional impairment [1]. The two predominant forms involving the heart are immunoglobulin light chain (AL) amyloidosis and transthyretin (ATTR) amyloidosis, the latter occurring in both hereditary (ATTRv) and wild-type (ATTRwt) variants [2]. Despite advances in non-invasive imaging, including bone-avid radiotracer scintigraphy and cardiac magnetic resonance, CA remains substantially underdiagnosed during life [1,2].

From a clinical perspective, delayed recognition is a central problem. Patients may present with non-specific manifestations that overlap with heart failure with preserved ejection fraction, hypertensive heart disease, ischemic heart disease, renal dysfunction, dysautonomia, syncope, psychiatric symptoms, or constitutional complaints. Classic echocardiographic “red flags” may be absent, incomplete, or subtle, whereas other clues—such as low ECG voltages, conduction abnormalities, atrial fibrillation, unexplained heart failure, abnormal serum protein studies, or renal involvement—may be present but not recognized as part of a systemic infiltrative disorder [3].

The medicolegal relevance of this diagnostic gap is substantial. CA may provide a natural cause of sudden death, yet it can be overlooked if

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amyloid deposition is interpreted as an incidental age-related finding or if targeted histological stains are not performed. Contemporary autopsy series and reviews challenge the older assumption that amyloid deposits are merely incidental in elderly decedents, showing that previously unrecognized CA may represent a clinically and forensically meaningful substrate for fatal arrhythmia, pulseless electrical activity (PEA), or acute cardiac decompensation [4–7].

The aim of this review is threefold: (1) to synthesize evidence on the prevalence of undiagnosed CA in autopsy series; (2) to review the incidence and mechanisms of sudden death in CA, including recent prospective rhythm-monitoring evidence; and (3) to define the role of autopsy and post-mortem diagnostic protocols in identifying CA as a cause of death. The accompanying previously reported illustrative case illustrates how multiple warning signs may be present during life but remain clinically unintegrated, leading to a post-mortem diagnosis of fatal systemic AL kappa amyloidosis.

2. Case presentation

The illustrative case reviewed here, previously reported in a concise case report [8], is an anonymized medicolegal case involving a woman in her late forties with no previously established diagnosis of amyloidosis. During the year preceding death, she developed a progressively worsening multisystem clinical picture characterized by diffuse musculoskeletal pain initially interpreted in a rheumatologic framework, progressive dysphagia, anorexia, severe weight loss, asthenia, impaired gait, depressed mood, and recurrent fear of imminent death. Several clinical contacts occurred before the terminal admission, but the symptoms remained diagnostically fragmented. Shortly before hospitalization, an internist recognized the complexity of the presentation and recommended additional investigations, including Bence-Jones proteinuria, but the available records did not show that this diagnostic pathway had been completed before the final deterioration.

At emergency presentation, the patient had hypotension, tachycardia, severe asthenia, dysphagia, reduced food intake, weight loss, and renal dysfunction. The ECG showed sinus tachycardia, low voltage in the limb leads, and nonspecific T-wave abnormalities. Laboratory tests documented renal impairment, anemia, inflammatory abnormalities, and later hypercalcemia. Despite these organic abnormalities, the clinical picture was mainly interpreted as a psychiatric disorder with depressive, hypochondriacal, or psychotic features, and the patient was admitted to a psychiatric ward. During hospitalization, persistent hypotension, worsening renal function, dysphagia, dyspnea, reduced oxygen saturation, poor oral intake, and progressive respiratory complaints were repeatedly documented. Serum protein electrophoresis subsequently showed a monoclonal kappa component, and immunoglobulin testing showed marked hypogammaglobulinemia; however, these findings were not promptly integrated with the ECG and renal abnormalities into a suspicion of systemic AL amyloidosis or plasma-cell dyscrasia.

In the final days, the patient repeatedly complained of air hunger, upper-airway secretions, and fear that she would not be able to breathe. A speech-language evaluation documented reduced orolingual motility, dysphonia, gurgling voice, and ineffective cough, supporting an organic impairment of swallowing and airway protection rather than a purely psychiatric explanation. During the last night she was described as repeatedly crying out that she could not breathe; she was later found unconscious, pulseless, and without spontaneous respiration, and resuscitation was unsuccessful.

Post-mortem examination and subsequent histological review were decisive. The heart weighed 240 g and did not show a uniformly classic gross appearance of restrictive amyloid cardiomyopathy, although a sclerotic plaque-like area was described in the posterior left ventricular wall extending toward the septum. Histology demonstrated cardiac amyloid involvement with interstitial and vascular/perivascular deposits, myocardial disarray, fibrotic and lipomatous replacement/

infiltration, and focal acute hypoxic injury. Additional deposits were identified in the pericardium, oropharynx, larynx, trachea, esophagus, thyroid, adipose tissue, lungs, omentum, and kidneys. Renal involvement included kappa light-chain cast nephropathy, consistent with excess monoclonal free kappa chains. The overall diagnosis was systemic AL kappa amyloidosis, probably related to an underlying plasma-cell dyscrasia, with relevant involvement of the upper aerodigestive tract, heart, and kidneys.

The medicolegal relevance of the case lies in the discrepancy between the documented ante-mortem warning signs and their clinical interpretation. Dysphagia, severe weight loss, renal dysfunction, low-voltage ECG, persistent hypotension, a monoclonal kappa component, dyspnea, ineffective cough, and air hunger were documented but were not integrated into a coherent systemic diagnosis. The death occurred in the context of advanced systemic AL kappa amyloidosis with cardiac and upper-aerodigestive involvement; however, the available records did not document the terminal rhythm. The case illustrates how autopsy can reconstruct an unrecognized multisystem disease process in an otherwise unexplained or insufficiently explained sudden death.

3. Materials and methods

Study design and search strategy. This systematic review was reported in accordance with PRISMA 2020 (Fig. 1). PubMed/MEDLINE was searched from database inception through 10 July 2026 using the free-text Boolean query: (amyloidosis AND (cardiac OR myocardium)) AND (autopsy OR post-mortem OR forensic pathology OR sudden death). No date limits were applied. Reference lists of eligible reports and relevant reviews were manually cross-checked to identify additional potentially eligible reports. Citation searching was used as a supplementary method, but additional records from this step were not separately quantified in the available flow data. The review was not prospectively registered.

Eligibility criteria. Reports were eligible if they were peer-reviewed, published in English, involved human cardiac amyloidosis (AL, ATTRwt, ATTRv, or an undefined subtype), and addressed at least one of the following: (1) prevalence or clinical recognition of CA at autopsy; (2) incidence or terminal mechanisms of sudden cardiac death; (3) autopsy-based cause-of-death or clinicopathological attribution; or (4) post-mortem histological or molecular detection and typing of cardiac amyloid.

- **Eligible report designs:** Retrospective or prospective cohorts, autopsy series, pathology and diagnostic-method studies, forensic or clinicopathological case reports and case series, and systematic reviews or meta-analyses reporting directly relevant autopsy or sudden-death evidence were eligible. The report was the unit of inclusion. Secondary reviews were used for contextual synthesis and were not combined numerically with primary datasets when evidence overlapped.
- **Exclusion criteria:** Reports were excluded if they were non-English publications; animal or in vitro studies; focused exclusively on extra-cardiac amyloidosis or lacked relevant post-mortem or sudden-death data; evaluated only in vivo imaging or therapy without an autopsy, pathology, or sudden-death correlation; or were conference abstracts, editorials, commentaries, preprints, or other non-peer-reviewed records.

Study selection. Records underwent title/abstract screening followed by full-text assessment against the eligibility criteria. The available flow data recorded no duplicate removals. The database search identified 1975 records; 1760 were excluded after title/abstract screening, and 215 full-text reports were assessed. Of these, 196 were excluded: 28 non-English reports; 40 reports without relevant post-mortem or sudden-death data, or with an exclusively extra-cardiac focus; 46 in vivo imaging or treatment reports without an autopsy

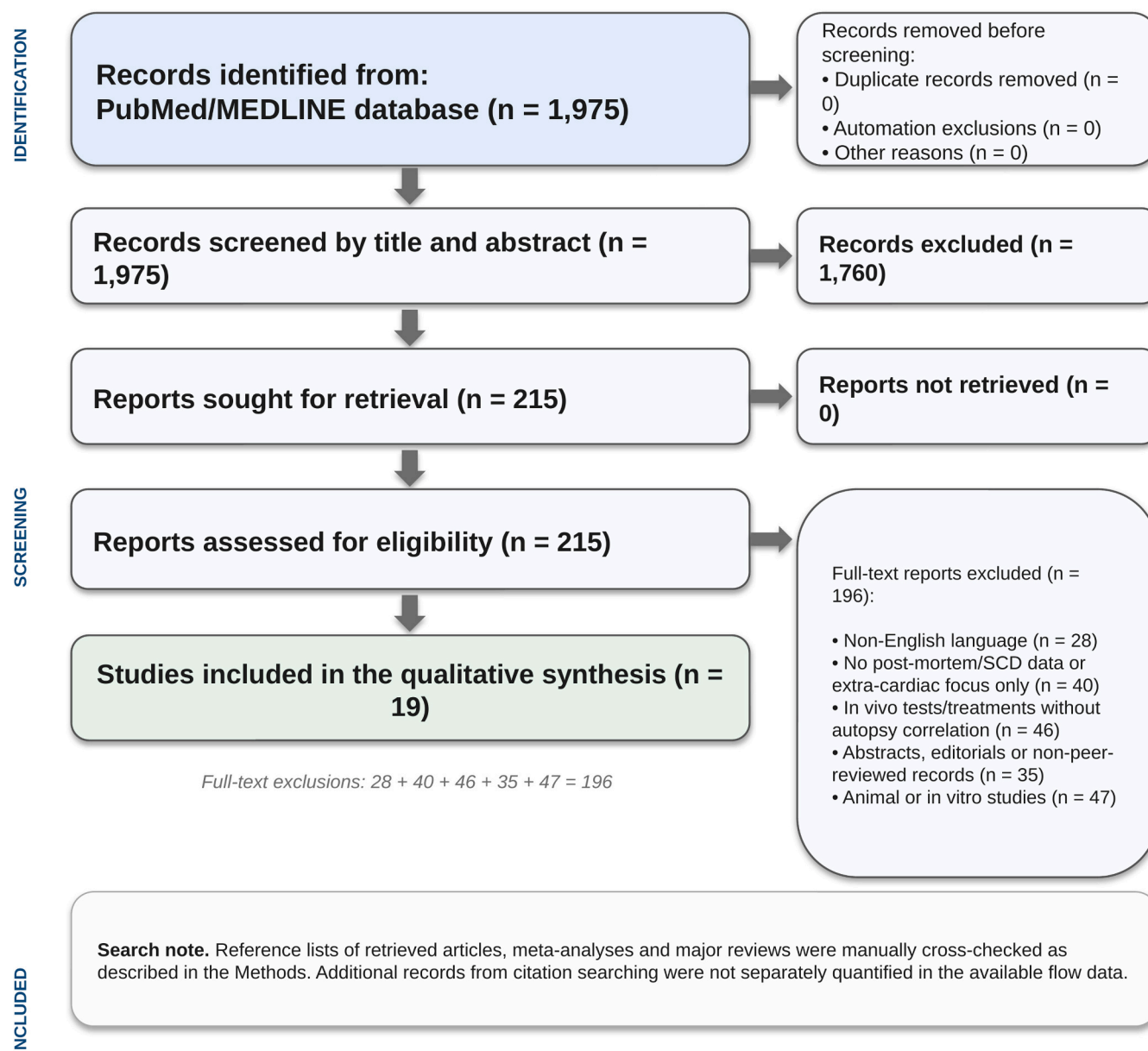


Fig. 1. PRISMA 2020 flow diagram based on the counts reported in the Methods. Reference lists were manually cross-checked; additional records from citation searching were not separately quantified in the available flow data.

correlation; 35 abstracts, editorials, commentaries, or non-peer-reviewed records; and 47 animal or in vitro studies. Nineteen eligible reports were included in the narrative synthesis. Records identified through citation searching were not separately quantified in the available flow data.

Data extraction. For each eligible report, the following information was extracted: first author, publication year, study design, sample size, population and clinical setting, amyloidosis subtype, prevalence of clinically undiagnosed CA in autopsy series, incidence and reported mechanisms of sudden death, and relevant macroscopic, histopathological, immunohistochemical, or molecular findings. For mixed-design evidence, primary datasets were used for outcome data; secondary reviews provided contextual synthesis, and overlapping evidence was not added to primary-study totals.

Data synthesis. Because the eligible evidence was heterogeneous in design and outcome definition, quantitative meta-analysis was not undertaken. Findings were synthesized narratively in three prespecified thematic groups: (1) clinical underdiagnosis and post-mortem

prevalence of cardiac amyloidosis; (2) incidence, risk factors, and mechanisms of sudden cardiac death; and (3) post-mortem diagnostic challenges and advanced histopathological or molecular techniques. [Table 1](#) reports study-level characteristics for all 19 eligible reports. No summary estimate was recalculated across overlapping primary and secondary evidence.

4. Results

4.1. Prevalence of undiagnosed cardiac amyloidosis at autopsy

Autopsy-based studies consistently show that CA is more frequent than clinically recognized. A systematic review and meta-analysis reported a pooled CA prevalence of 21% (95% CI 7–39%) across four autopsy series of unselected older adults; study-specific inclusion ages were ≥ 75 years, >80 years, >85 years, and 90–105 years [2]. These data are consistent with epidemiological reviews emphasizing that amyloid deposits are increasingly identified in older populations and

Table 1

Characteristics of the 19 reports included in the narrative synthesis. The table summarizes study design, population, amyloidosis subtype, prevalence of undiagnosed cases, incidence and mechanisms of sudden cardiac death (SCD), and main pathological or medicolegal findings. The prior case report cited for transparency [8] was not counted among the 19 eligible review reports. Reports are grouped into three thematic categories: (1) clinical underdiagnosis and post-mortem prevalence; (2) incidence, risk factors, and mechanisms of SCD; and (3) post-mortem diagnostic challenges and advanced techniques.

Thematic area	Reference	Study design	Population/subtype	Main findings	Medicolegal or diagnostic relevance
Epidemiology/autopsy prevalence	Aimo et al. (2022) [2]	Systematic review and meta-analysis	Screening studies; mixed CA subtypes	Reported substantial under-recognition of CA and autopsy prevalence up to 21% in unselected elderly individuals. CA identified in 5.3% of autopsies; 91.3% undiagnosed before death.	Supports the concept that the epidemiological burden of CA is underestimated during life.
Epidemiology/autopsy prevalence	Baschong et al. (2025) [9]	Retrospective autopsy cohort	1972 adult autopsies; predominantly ATTR	CA identified in 5.3% of autopsies; 91.3% undiagnosed before death.	Demonstrates the scale of missed clinical diagnosis and the value of systematic autopsy review.
Epidemiology/autopsy prevalence	Maccio et al. (2025) [3]	Autopsy-based analysis	Complete whole-body autopsies	Clinically undiagnosed CA correlated with age and cardiovascular/renal comorbidity.	Shows how CA may be masked by common comorbid conditions.
Epidemiology/autopsy prevalence	Cianci et al. (2024) [1]	Review/epidemiological synthesis	ATTR cardiac amyloidosis	Summarized evidence from in vivo data and autopsic series.	Highlights the evolving epidemiology of ATTR-CA and the importance of autopsy data.
Epidemiology/autopsy prevalence	Krishnappa et al. (2019) [10]	Retrospective autopsy cohort	1083 autopsies; isolated cardiac amyloidosis	Isolated CA found in 3.1% overall and 8.2% of individuals aged >80 years; associated with atrial fibrillation.	Links clinically unrecognized cardiac amyloid with an arrhythmic phenotype.
Sudden death/mechanisms	Kharoubi et al. (2022) [7]	Clinical cohort	AL, ATTRwt, ATTRv	SCD accounted for a relevant proportion of cardiovascular deaths, peaking in AL amyloidosis.	Frames SCD as a major mode of death in CA.
Sudden death/mechanisms	D'Errico et al. (2020) [11]	Review	AL cardiac amyloidosis	Reviewed sudden-death mechanisms in AL amyloidosis, including PEA and conduction disorders.	Relevant to clinicians and pathologists evaluating unexpected death.
Sudden death/mechanisms	De Frutos et al. (2024) [12]	Clinical cohort/incidence study	AL and ATTR CA	Reported subtype-related differences in SCD incidence and predictors.	Supports risk stratification and subtype-specific interpretation.
Sudden death/mechanisms	Ichimata et al. (2021) [5]	Forensic autopsy series	Clinically undiagnosed sporadic ATTR	Reported SCD in a substantial proportion of forensic autopsy cases.	Directly relevant to forensic recognition of undiagnosed ATTR-CA.
Sudden death/mechanisms	Ioannou et al. (2026) [13]	Prospective rhythm-monitoring study	110 treatment-naïve CA patients; ATTRwt-CM, ATTRv-CM, AL-CA	Bradyarrhythmias requiring pacemaker in 17.3%; new-onset AF in 28.2%; terminal rhythm predominantly PEA.	Shows that clinically significant arrhythmias are common, frequently asymptomatic, and closely related to myocardial amyloid burden.
Sudden death/mechanisms	Sperry et al. (2023) [14]	Case series	Four patients with AL cardiac amyloidosis	Witnessed PEA arrests associated with vasovagal syncope and severe autonomic dysfunction.	Illustrates non-shockable terminal events and dysautonomia-related risk.
Post-mortem diagnosis	Mueller et al. (2000) [4]	Clinicopathological/autopsy series	Obstructive intramural coronary amyloidosis	Diagnosis was difficult during life and established at autopsy or explanted-heart examination.	Supports post-mortem identification of vascular amyloid involvement.
Post-mortem diagnosis	Tan and Byard (2024) [6]	Forensic autopsy series with literature review	16 cardiac amyloid cases over 20 years; mixed types	Cardiac amyloid contributed to the lethal episode in 11 cases and was incidental in five.	Emphasizes clinicopathological distinction among cause, contributing condition, and incidental finding.
Post-mortem diagnosis	Flood et al. (2021) [15]	Case report/review	Cardiac amyloid after cardiac surgery	Amyloid may contribute to cardiac dysfunction and remain unrecognized clinically.	Warns against dismissing amyloid as incidental.
Post-mortem diagnosis	Cazzaniga et al. (2025) [16]	Digital pathology study	Cardiac amyloidosis tissue analysis	Congo red fluorescence improved digital pathology workflow.	Relevant to reproducible post-mortem amyloid detection.
Post-mortem diagnosis	Larsen et al. (2016) [17]	Histological/proteomic analysis	108 cardiac amyloid cases	Correlated deposition patterns with amyloid subtype.	Supports the need for subtyping beyond morphology alone.
Post-mortem diagnosis	Rancati et al. (2018) [18]	Forensic case report	Lethal cardiac amyloidosis	Modified Congo red technique enabled amyloid detection in a forensic case.	Highlights technical pitfalls in post-mortem staining.
Post-mortem diagnosis	Hung et al. (2025) [19]	Clinicopathological case report	Cardiac amyloidosis with discordant IHC	LC-MS/MS resolved subtype after inconclusive immunohistochemistry.	Supports proteomic confirmation when immunostaining is ambiguous.
Post-mortem diagnosis	Kawai et al. (2025) [20]	Autopsy case report	ATTR obstructive intramural coronary amyloidosis	Autopsy revealed microvascular ATTR deposition despite absent hypertrophy or apical sparing ante mortem.	Shows that vascular-predominant CA may be missed by conventional clinical imaging.

that autopsy series remain essential for estimating the true burden of disease [1].

In a large retrospective autopsy cohort of 1972 adults, CA was identified in 5.3% of cases, and 91.3% of affected individuals had not been diagnosed during life [9]. Complete autopsy cohorts likewise show that clinically unrecognized CA is associated with advanced age and common cardiovascular or renal comorbidities, including hypertension, chronic kidney disease, hypertensive cardiomyopathy, and coronary artery disease [3]. In a separate series of 1083 autopsies, isolated CA was found in 3.1% overall and in 8.2% of individuals aged over 80 years; affected individuals had a higher likelihood of atrial fibrillation [10]. These findings indicate that CA may be masked by or misattributed to more common clinical conditions.

4.2. Sudden cardiac death: incidence and mechanisms in CA

Sudden death is a major mode of death in CA. Clinical and pathological studies indicate that SCD accounts for a substantial proportion of cardiovascular deaths, with a particularly high burden in AL amyloidosis [7,11]. Reported mechanisms include PEA, severe bradyarrhythmias, conduction block, electromechanical dissociation, dysautonomia-related events, atrial fibrillation, and, less frequently, sustained ventricular tachyarrhythmias [10–12,14]. This mechanistic profile helps explain why implantable cardioverter-defibrillators may fail to prevent death when the terminal event is non-shockable [11].

The EXCALIBUR study provides particularly relevant prospective evidence. Ioannou et al. enrolled 110 treatment-naïve patients with newly diagnosed CA, including 43 with ATTRwt-CM, 20 with ATTRv-

CM, and 47 with AL-CA, and used implantable loop recorders after comprehensive phenotyping with cardiac magnetic resonance [13]. Clinically significant arrhythmias were common and frequently asymptomatic. Bradyarrhythmias meeting a Class I indication for pacemaker implantation occurred in 17.3% of patients and were more frequent in ATTR-CM than in AL-CA. New-onset atrial fibrillation occurred in 28.2% of patients without previous atrial fibrillation. During follow-up, 21 patients died; the terminal rhythm was uniformly PEA in ATTR-CM, whereas in AL-CA PEA accounted for 81.8% of terminal rhythms and sustained ventricular arrhythmias for 18.2% [13].

These findings are directly relevant to the medicolegal interpretation of sudden death. They support a more precise understanding of the diagnostic gap: CA is not necessarily “silent” in the strict sense; rather, warning signs may be present but insufficiently recognized, particularly conduction disease, low ECG voltages, arrhythmias, dysautonomia, unexplained decompensation, renal impairment, or systemic symptoms. In this context, autopsy can transform an apparently unexplained or misattributed death into a defined natural death due to amyloid cardiomyopathy.

4.3. Post-mortem diagnostic challenges in forensic pathology

Autopsy may be the only means of establishing CA when clinical imaging or clinical suspicion has failed. Obstructive intramural coronary amyloidosis can mimic ischemic heart disease while coronary angiography remains normal or non-diagnostic; in classic clinicopathological series, the diagnosis was established only at autopsy or after examination of the explanted heart [4]. A recent autopsy report described vascular-predominant ATTR amyloid causing microvascular obstruction, bradycardia, and acute heart failure despite the absence of ventricular hypertrophy or apical sparing ante mortem [20]. Similar considerations apply when cardiac dysfunction or low-output states are attributed to ischemic, valvular, hypertensive, or perioperative disease while amyloid infiltration remains unrecognized during life [15].

The post-mortem diagnosis of CA requires targeted histology. Congo red staining with apple-green birefringence under polarized light remains a cornerstone, but cadaveric samples may be affected by prolonged fixation, decomposition, and technical variability. Modified Congo red protocols may be necessary in forensic material [18]. Digital pathology introduces additional challenges, because birefringence may be difficult to reproduce on whole-slide images; Congo red fluorescence has been proposed to improve sensitivity and workflow reproducibility [16].

Once amyloid is detected, subtyping is essential. Differentiating AL from ATTR has implications for pathogenesis, family screening, clinical interpretation, and medicolegal conclusions. Morphological patterns may provide useful clues, but morphology alone is insufficient [17]. Immunohistochemistry is useful but may be limited by false-positive cross-reactivity or false-negative staining; ambiguous cases should therefore be resolved using advanced proteomic techniques, particularly laser microdissection followed by LC-MS/MS when available [19].

5. Discussion

The findings of this review indicate a discrepancy between the clinical recognition of CA and its prevalence in autopsy series, particularly in the context of SCD. Contemporary studies show that CA may remain undiagnosed during life, especially in older patients and in AL amyloidosis. Sudden death mechanisms are multifactorial and include PEA, severe bradyarrhythmias, conduction disease, ventricular arrhythmias, and dysautonomia-related events. In contrast to other cardiomyopathies, non-shockable rhythms appear to account for a substantial proportion of terminal events in CA.

From a forensic perspective, the identification of occult CA at autopsy may provide a medically supported natural cause of death when imaging and the clinical history did not establish the diagnosis. Fatal

acute heart failure or PEA initially attributed to broad diagnostic categories may, after post-mortem examination, be associated with previously unrecognized amyloid involvement of the myocardium, microvasculature, or conduction system.

In forensic practice, clinical information may be incomplete or unavailable, and occult CA may not be apparent on gross examination. Cardiac amyloid can also be encountered in deaths classified as unnatural, including fatal blunt trauma, where its role must be distinguished as causal, contributory, or incidental [6]. Accordingly, representative cardiac tissue should be examined histopathologically whenever feasible, particularly in older decedents and in deaths following falls or other accidents, even when gross cardiac findings are non-specific. This approach may identify an occult cardiac process that plausibly contributed to the circumstances of death while avoiding over-attribution when amyloid is incidental.

The previously reported illustrative case shows how a systemic disease may remain unrecognized when its manifestations are interpreted separately. The patient had progressive dysphagia, severe weight loss, renal impairment, persistent hypotension, low-voltage ECG, a monoclonal kappa component, dyspnea, ineffective cough, and progressive clinical decline. These findings were present during life but were not integrated into a single organic diagnosis. The psychiatric interpretation of part of the presentation contributed to obscuring a serious systemic organic disease.

From a forensic perspective, this type of case demonstrates the essential role of autopsy in unexplained or poorly explained sudden death. Post-mortem examination does not merely confirm a suspected diagnosis; in many cases it reconstructs the entire clinical meaning of events that remained unclear during life. In the present case, histological and immunohistochemical examination documented systemic AL kappa amyloidosis with involvement of the upper aerodigestive tract, heart, pericardium, thyroid, adipose tissue, and kidneys, together with kappa light-chain cast nephropathy. These findings allowed the clinical course, the terminal cardiorespiratory collapse, and the missed diagnostic opportunities to be interpreted within a coherent pathological framework.

These findings support a standardized and comprehensive post-mortem diagnostic approach encompassing clinical and forensic pathology in selected cases of unexplained sudden death. Identification and typing of hereditary ATTR variants may inform cascade evaluation of relatives. In the medicolegal setting, a documented post-mortem work-up can also assist in distinguishing natural disease from alternative causes and in evaluating questions of medical liability.

A rigorous forensic protocol should include:

- Detailed macroscopic evaluation: a thorough morphological analysis of the heart is essential to identify the increased ventricular wall thickness and “rubbery” consistency characteristic of amyloid deposits.
- Mapped histological sampling: myocardial samples should be obtained from representative areas of both ventricles and the septum, systematically including the cardiac conduction system and intramural vessels where amyloid may deposit focally.
- Specific staining techniques: standard hematoxylin-eosin staining alone is insufficient; Congo red staining should be performed and evaluated under polarized light to confirm apple-green birefringence. In forensic material, modified protocols may be considered when prolonged formalin fixation or decomposition affects staining quality.
- Molecular subtyping: immunohistochemistry contributes to sub-classification (AL vs. ATTR), while inconclusive cases may require proteomic techniques such as laser microdissection followed by mass spectrometry, where available.

The post-mortem diagnosis of CA may also have implications for surviving family members. Identification of hereditary ATTR variants can support cascade evaluation and, where appropriate, earlier clinical

assessment and treatment.

Several limitations should be considered. The search was limited to PubMed/MEDLINE and English-language peer-reviewed reports, and records identified through citation searching were not quantified separately in the available flow data. The evidence base comprised heterogeneous report types, including autopsy cohorts, clinical cohorts, diagnostic-method studies, reviews, and case reports; therefore, quantitative pooling and formal certainty grading were not performed. Secondary reviews were used for context and were not added to primary-study totals when evidence overlapped.

6. Conclusion

Cardiac amyloidosis remains a significantly underdiagnosed cause of sudden death. Contemporary autopsy studies, arrhythmic investigations, and forensic case reports converge on the same conclusion: fatal CA is often missed not because warning signs are necessarily absent, but because they are fragmented, misattributed, or insufficiently investigated. The EXCALIBUR study reinforces the mechanistic plausibility of sudden death through asymptomatic arrhythmias and predominantly non-shockable terminal rhythms. The previously reported illustrative case further demonstrates that systemic AL kappa amyloidosis may present with multiple warning signs, including renal dysfunction, low-voltage ECG, monoclonal kappa component, dysphagia, dyspnea, and persistent hypotension, yet remain clinically unrecognized until post-mortem examination. Standardized autopsy protocols, including Congo red staining, immunohistochemical or proteomic amyloid typing, and systematic sampling of the myocardium, vessels, conduction system, and clinically relevant extracardiac sites, should therefore be implemented in unexplained sudden death whenever clinical, macroscopic, or histological features raise suspicion for CA.

Informed consent statement

Patient consent was waived due to the nature of the study involving deceased subjects under judicial investigation. The authors were unable to contact the next-of-kin, but strict anonymization measures were applied. Data processing and handling were performed in full compliance with the Regulation (EU) 2016/679 (GDPR) and the Italian Legislative Decree 196/2003, as amended by Legislative Decree 101/2018.

Institutional review board statement

The study was conducted in accordance with the Declaration of Helsinki. Ethical review and approval were waived for this study because no experimental intervention was performed. The biological material was explicitly collected for institutional and judicial purposes, and all samples and data were fully anonymized.

Ethics declaration

The authors have NOT obtained informed consent from participants or their legal representatives. Patient consent was waived due to the nature of the study involving deceased subjects under judicial investigation. The authors were unable to contact the next-of-kin, but strict anonymization measures were applied. The data presented in this study are available on request from the corresponding author. The data are not publicly available due to investigative secrecy.

This study included organ or tissue donors.

This study includes human biological material and consent was obtained by donors, or their next of kin or legal representatives, for use in this study and for publication of the article. The samples used in this research were not sourced from executed prisoners or prisoners of conscience.

This study was performed in compliance with relevant laws, regulatory frameworks and guidelines where the research took place.

Ethics committee approval was not required under relevant laws and institutional guidelines. Patient consent was waived due to the nature of the study involving deceased subjects under judicial investigation. The authors were unable to contact the next-of-kin, but strict anonymization measures were applied. Data processing and handling were performed in full compliance with the Regulation (EU) 2016/679 (GDPR) and the Italian Legislative Decree 196/2003, as amended by Legislative Decree 101/2018.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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