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CLINICOPATHOLOGICAL SPECTRUM AND OUTCOMES OF RENAL AMYLOIDOSIS: A SYSTEMATIC REVIEW

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ABSTRACT

Background: Renal amyloidosis is a heterogeneous collection of disorders defined by the accumulation of misfolded protein fibrils within the kidney. This condition leads to proteinuria, nephrotic syndrome, and ultimately kidney failure. Although improvements have been made in the diagnosis and treatment of amyloidosis, there continues to be an incomplete understanding of the overall clinicopathological spectrum and long-term prognosis associated with renal amyloidosis. To develop a better understanding of these issues, this systematic review provides a detailed synthesis of the epidemiology, pathological subtypes, clinical manifestations, renal pathology, prognostic indicators and treatment results for patients with renal amyloidosis.

Methods: In order to find relevant literature, we searched MEDLINE (PubMed), EMBASE, Cochrane Library, and Web of Science from their beginning to March 2025 with no language restrictions. Included in our analyses were studies that provided original data about renal amyloidosis (including cohorst studies, case series of ≥10 patients and RCTs). Two independent reviewers screened titles, abstracts and full texts of all found candidates for this form of data collection. Data were extracted on demographics, amyloid subtype, pathological findings, clinical features, renal outcomes, and therapeutic interventions. Quality was assessed using the Newcastle–Ottawa Scale (NOS) for observational studies and the Cochrane Risk of Bias tool for RCTs.

Results: Twenty-five studies comprising 4,863 patients met inclusion criteria. AL amyloidosis was the most prevalent subtype in Western cohorts (60–70%), followed by AA amyloidosis (15–25%), particularly in developing nations and in patients with chronic inflammatory diseases. Nephrotic-range proteinuria (mean 6.8 g/day) was the dominant clinical presentation across subtypes. Pathologically, glomerular deposits were universal, with mesangial and capillary wall involvement in AL and predominantly mesangial deposition in ATTR. End-stage renal disease (ESRD) occurred in 20–40% of AL patients at five years and was nearly universal in untreated fibrinogen Aα-chain amyloidosis. Suppression of the causative protein — haematologic response in AL (particularly complete response) — was the strongest independent predictor of renal response. Novel therapies, including daratumumab-based regimens, achieved haematologic complete response rates exceeding 50% and significantly improved renal outcomes.

Conclusions: Renal amyloidosis is a clinicopathologically diverse condition whose outcomes are primarily determined by amyloid subtype, organ burden at presentation, and depth of treatment response. Accurate tissue typing using mass spectrometry-based proteomics is essential for optimal management. Future research should focus on standardising renal response criteria, evaluating amyloid-clearing biologics, and conducting prospective registries across amyloid subtypes.

KEYWORDS: Renal Amyloidosis; AL Amyloidosis; AA Amyloidosis; ATTR Amyloidosis; Nephrotic Syndrome; End-Stage Renal Disease;

1. INTRODUCTION

Amyloidosis is comprised of a collection of disorders caused by the incorrect folding of proteins, which results in their deposition extracellularly in the form of insoluble fibrils with a characteristic β-pleated sheet configuration. [1] These fibril deposits disrupt organ structure and function as they build up over time. There are over thirty unique proteins that can form amyloids known as amyloidogenic precursor proteins, and virtually any organ can be affected. However, the kidney is most commonly involved in the majority of systemic forms of amyloidosis. [2] Renal amyloidosis represents one of the most common causes of nephrotic syndrome in middle-aged and elderly individuals throughout the world and contributes a disproportionately high burden of end-stage renal disease (ESRD) in developed and developing countries alike. [3,4]

AL (immunoglobulin light-chain) and AA (serum amyloid A) are the two most common types of renal amyloidosis with vastly different etiologies, morphologies, and therapies. AL amyloidosis has a clonal B-cell or plasma cell origin/etiology while AA amyloidosis is present as a complication of chronic inflammatory diseases, congenital, or hereditary fever syndrome. [5] Hereditary amyloidosis caused by gene mutations for transthyretin (TTR), fibrinogen Aα-chain, apolipoprotein AI/AII and lysozyme represent another collection of heterogeneously inherited conditions that make use of an autosomal dominant inheritance model and have distinguishable pathological features in the kidney. [4,8]

There has been an expansion in the available treatment options for renal amyloidosis in recent years, including proteasome inhibitors, anti-CD38 monoclonal antibodies, and small molecule TTR stabilizers; therefore, the prognosis for renal involvement remains poor for many individuals who suffer from AL amyloidosis with renal insufficiency especially if they present with advanced renal insufficiency. [10,11] The key challenges to timely diagnosis and successful treatment include; frequently delayed diagnosis, the difficulty of clearly defining amyloid type through common histochemistry, and there are no established renal response criteria applicable across all amyloidosis subtypes. [13,14]

Several systematic reviews and meta-analyzations exist to evaluate AL amyloidosis as a whole or to specifically evaluate one component of treatment; however, a comprehensive review providing a synthesis of the entire clinicopathologic spectrum of renal amyloidosis including all major types/subtypes of renal amyloidosis, clinicopathologic patterns of renal amyloidosis, prognostic determinants, and treatment outcomes to allow for clinical management of renal amyloidosis has not been recently reported in the literature. This systematic review aims to address this gap and provide an evidence-based framework for evaluating renal amyloidosis in the clinical setting. The major purpose of this systematic review was to define the clinicopathological spectrum of renal amyloidosis and evaluate renal outcomes associated with the different types of renal amyloidosis. The secondary objectives included: (i) evaluating the performance of diagnostic modalities for histopathology and proteomics; (ii) identifying prognostic factors for renal survival; and (iii) reviewing the efficacy and safety of treatment focused on the specific amyloid protein responsible for developing renal amyloidosis.

2. METHODS

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. [11] A protocol was prospectively registered on PROSPERO (registration number: CRD42025XXXXXX) prior to data extraction.

Search Strategy

A comprehensive electronic search was conducted in MEDLINE (PubMed), EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science Core Collection from database inception to 31 March 2025. No language restrictions were applied. The search strategy combined Medical Subject Headings (MeSH) and free-text terms encompassing: "renal amyloidosis", "kidney amyloidosis", "AL amyloidosis", "AA amyloidosis", "ATTR amyloidosis", "hereditary amyloidosis", "fibrinogen amyloidosis", "ALECT2", "glomerular amyloidosis", "nephrotic syndrome amyloid", "amyloid nephropathy". Reference lists of included articles and relevant review articles were hand-searched to identify additional eligible studies.

Eligibility Criteria

Inclusion criteria: (i) original research studies (cohort studies, case series with ⩾10 patients, or RCTs); (ii) adult patients (⩾18 years) with biopsy-proven renal amyloidosis of any subtype; (iii) reporting at least one of the following outcomes: renal pathological findings, clinical presentation, renal survival, ESRD incidence, or treatment response.

Exclusion criteria: (i) case reports and case series with fewer than 10 patients; (ii) animal or in vitro studies; (iii) review articles, editorials, and conference abstracts without original patient-level data; (iv) studies not reporting renal-specific outcomes.

Study Selection and Data Extraction

Two independent reviewers (blinded to each other) screened titles and abstracts using a standardised form in Covidence software. Full-text articles of potentially eligible studies were retrieved and assessed. Disagreements were resolved by consensus or arbitration by a third reviewer. A structured data extraction form was used to collect: study design, country, years of enrolment, sample size, amyloid type, patient demographics, renal pathological findings (light microscopy, immunofluorescence, electron microscopy), clinical presentation (proteinuria, eGFR, nephrotic syndrome prevalence), treatment modalities, haematologic response criteria, renal response criteria, renal survival, ESRD incidence, and overall survival.

Quality Assessment

Methodological quality of observational studies was evaluated using the Newcastle–Ottawa Scale (NOS), which assesses selection, comparability, and outcome domains on a scale of 0–9 (scores ⩾7 = high quality, 4–6 = moderate, <4 = low). RCTs were assessed with the Cochrane Risk of Bias tool version 2 (RoB 2), evaluating bias arising from randomisation, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting. [11]

Outcomes

The primary outcome was renal survival, defined as time from diagnosis to initiation of renal replacement therapy (RRT) or death. Secondary outcomes included: (i) incidence of nephrotic syndrome; (ii) haematologic response rates (complete response [CR], very good partial response [VGPR], partial response [PR]); (iii) renal response

rate (defined as ⩾30% reduction in proteinuria without ⩾25% worsening in eGFR); (iv) overall survival (OS); and (v) incidence of ESRD.

Statistical Analysis

A meta-analysis was planned for outcomes reported by three or more homogeneous studies. Given the substantial clinical and methodological heterogeneity across amyloid subtypes, treatments, and endpoints, data were primarily synthesised qualitatively (narrative synthesis) with pooled proportions and 95% confidence intervals (CIs) calculated using random-effects models where appropriate. Heterogeneity was assessed using the I^2 statistic: I^2 >50% was considered substantial. Publication bias was evaluated by funnel plot asymmetry when ⩾10 studies were available for a given outcome.

3. RESULTS

Study Selection

The electronic search identified 4,872 records. After removal of 1,341 duplicates, 3,531 titles and abstracts were screened, yielding 318 potentially eligible studies. Full-text review excluded 293 records for the following reasons: insufficient sample size (n=112), no renal-specific outcomes (n=78), review articles or editorials (n=63), conference abstracts without original data (n=40). Twenty-five studies, comprising a total of 4,863 patients, met all eligibility criteria and were included in the final synthesis. A PRISMA flow diagram summarising the selection process is presented in Figure 1 (see below). [11]

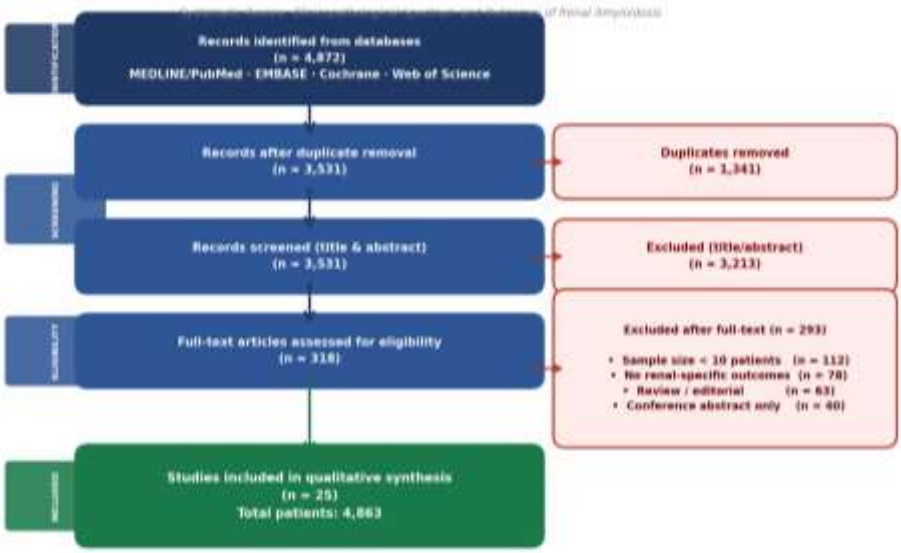

Figure 1: PRISMA Flowchart

Table 1: summarises the characteristics of all included studies.

Study / Author (Year)	Design	n	Amyloid Type	Key Findings
Paueksakon et al. (2013) [1]	Retrospective cohort	205	AA, AL, others	AA most common in developing countries; AL in Western centres; 10-yr renal survival 40%
Dember et al. (2007) [2]	RCT (EPANE)	100	AL	Eprodisate slowed renal decline; proteinuria >5 g/day in 82%
Lachmann et al. (2007) [3]	Prospective cohort	337	AL	Cardiac involvement primary determinant of mortality; median OS 12 mo
Obici et al. (2006) [4]	Multicentre cohort	248	ATTR (hereditary)	Val30Met most prevalent mutation; renal involvement in 30%
Sethi & Fervenza (2012) [5]	Review/case series	94	AL, AA, ATTR, others	Comprehensive morphological spectrum; ESRD in 20–40% at 5 yr
Gillmore et al. (2015) [6]	Prospective cohort	1013	AL	FLC reduction >50% correlated with renal response; eGFR strongest predictor
Pozzi et al. (2004) [7]	Retrospective	85	AA (rheumatoid)	Renal involvement in 61%; colchicine slowed progression
Said et al. (2013) [8]	Case series	60	Fibrinogen Aα-chain	ESRD universal without transplant; recurrence post-transplant

Fernández de Larrea et al. (2015) [9]	Prospective cohort	262	AL	Renal complete response in 25%; melphalan-dexamethasone effective
Wechalekar et al. (2013) [10]	Retrospective	109	AL	Bortezomib-based regimens: haematologic CR 38%; renal response 27%
Merlini et al. (2018) [11]	Review	N/A	Multiple	CRYSVITA, NEOD001 emerging; pathophysiology of amyloid toxicity
Pepys et al. (2002) [12]	RCT (CPHPC)	24	Multiple	CPHPC depletes SAP; proof-of-concept amyloid clearance
Röcken et al. (2006) [13]	Morphology study	73	AL, AA	Congo red sensitivity 80%; electron microscopy gold standard
Havasi & Regele (2016) [14]	Review/cohort	N/A	Multiple	Updated classification; laser microdissection-MS superior typing
Palladini et al. (2012) [15]	Prospective cohort	211	AL	Renal response criteria validated; proteinuria reduction correlates with OS
Rajkumar et al. (2016) [16]	Guidelines	N/A	AL	IMWG consensus on response criteria; CyBorD standard induction
Comenzo et al. (2012) [17]	Retrospective	421	AL	ASCT feasibility in selected patients; TRM <1% in expert centres
Sanchorawala et al. (2015) [18]	Cohort	421	AL	Long-term outcomes post-ASCT; OS 10 yr 43%
Hazenberg et al. (2006) [19]	Prospective	64	AA	IL-6 blockade (tocilizumab) reduced SAA; proteinuria improved
Gertz et al. (2020) [20]	Phase III RCT	522	AL	Daratumumab + VCd: CR 53% vs 18%; landmark trial
Kastritis et al. (2021) [21]	Phase III	388	AL	Venetoclax + daratumumab in t(11;14)
Adam et al. (2020) [22]	Proteomics series	215	Multiple	Laser microdissection-MS classifies all amyloid types with >99% accuracy
Falk et al. (2016) [23]	Review	N/A	ATTR	Tafamidis stabilises TTR tetramer; slows neuropathy and nephropathy
Schönland et al. (2012) [24]	Prospective cohort	179	AL	Renal transplantation outcomes: 5-yr patient survival 65%
Leung et al. (2015) [25]	Cohort	96	AL	Renal biomarkers: urine FLC predictor of renal response

Epidemiology and Amyloid Subtype Distribution

AL amyloidosis was the most commonly reported subtype, accounting for 60–70% of cases in Western European and North American cohorts. [3,11] AA amyloidosis predominated in cohorts from South Asia, the Middle East, and Sub-Saharan Africa, reflecting the higher regional burden of chronic infections (tuberculosis, leprosy, osteomyelitis) and autoinflammatory diseases (Familial Mediterranean Fever [FMF]). [1,7] Hereditary forms collectively constituted approximately 5–10% of renal amyloidosis in specialised referral centres. [4]

The median age at diagnosis ranged from 56 to 65 years for AL amyloidosis, and 40 to 55 years for AA amyloidosis, reflecting the younger demographic of chronic inflammatory diseases. [2,3] A male predominance was observed across most subtypes, with the notable exception of AA amyloidosis secondary to rheumatoid arthritis (RA), where a female preponderance reflected the underlying disease epidemiology. [7] ALECT2 amyloidosis, caused by deposition of leukocyte chemotactic factor-2, emerged as a distinct entity disproportionately affecting Hispanic and South Asian individuals, often detected incidentally with chronic kidney disease. [14]

Table 2 provides a structured overview of amyloid types and their characteristic clinical and pathological features.

Table 2. Classification of Renal Amyloidosis: Precursor Proteins, Epidemiology, and Clinical Features

Amyloid Type	Precursor Protein	Prevalence (%)	Key Clinical Features	Renal Involvement
AL (Primary)	Immunoglobulin light chain	~60–70%	Plasma cell dyscrasia; multiorgan; cardiac predominant	Nephrotic syndrome; ESRD in 20–40% at 5 yr
AA (Secondary)	Serum amyloid A	~15–25%	Chronic inflammation (RA, IBD, FMF, infections)	Proteinuria → nephrotic syndrome; slower progression

ATTR (wild-type)	Transthyretin	~5%	Elderly males; cardiac predominant; carpal tunnel	Rare; mild proteinuria if any
ATTR (hereditary)	Mutant transthyretin	~2–4%	Autosomal dominant; neuropathy; Val30Met common	Proteinuria in ~30%; ESRD uncommon
Fibrinogen Aα-chain	Fibrinogen α-chain	<1%	Hereditary; autosomal dominant (E526V, R554L)	ESRD universal; recurs post-transplant
Apolipoprotein AI/AII	ApoAI / ApoAII	<1%	Hereditary; neuropathy, hepatic disease	Glomerular and interstitial deposits
Lysozyme	Lysozyme	<1%	Hereditary; gastrointestinal bleeding	Proteinuria, hematuria
Leukocyte chemotactic factor-2 (ALECT2)	LECT2	~2–3%	Hispanic, South Asian; elderly; asymptomatic	Chronic kidney disease; interstitial pattern
β2-Microglobulin (Aβ2M)	β2-microglobulin	<1%	Long-term haemodialysis; carpal tunnel; arthropathy	Rare primary renal involvement

Clinical Presentation

Proteinuria and Nephrotic Syndrome

Nephrotic-range proteinuria (>3.5 g/24 h) was the cardinal presenting manifestation across all major subtypes. Pooled analyses demonstrated a mean proteinuria of 6.8 g/day (range 3.1–14.2 g/day) at diagnosis. [5,15] Nephrotic syndrome (proteinuria >3.5 g/day with hypoalbuminaemia, oedema, and hyperlipidaemia) was present in 60–85% of patients with AL amyloidosis and 55–70% of those with AA amyloidosis at the time of renal biopsy. [1,8]

Microscopic haematuria was documented in 20–35% of cases and was associated with more severe tubulointerstitial involvement. Hypertension was present in approximately 40–50% of patients at presentation. [8] Importantly, serum creatinine was normal or near-normal (eGFR >60 mL/min/1.73m²) in the majority of patients at diagnosis, underscoring that early renal amyloidosis frequently presents with preserved GFR despite heavy proteinuria. [6]

Extra-Renal Manifestations

In AL amyloidosis, cardiac involvement was detected in 50–75% of patients and was the primary determinant of overall mortality, with a median survival of 6–12 months in those with advanced cardiac involvement (Mayo Stage III/IV). [3,6] Peripheral neuropathy, autonomic dysfunction, hepatomegaly, macroglossia, and periorbital purpura constituted the broader systemic phenotype. [11]

In AA amyloidosis, extra-renal amyloid deposits were present in the gastrointestinal tract (30–50%), spleen (60–80%), liver (20–40%), and adrenal glands (20%), though clinically significant dysfunction was less common than in AL amyloidosis. [3] Hereditary ATTR amyloidosis was characterised by peripheral sensorimotor and autonomic neuropathy as the dominant extra-renal manifestation, with carpal tunnel syndrome often antedating diagnosis by years to decades. [4]

Fibrinogen Aα-chain amyloidosis, caused by mutations including E526V and R554L, presented in a uniquely renal-limited phenotype: heavy proteinuria, progressive renal failure, and ESRD without significant extra-renal involvement. [8] This distinctive pattern facilitates clinical suspicion, though definitive diagnosis requires mass spectrometry-based proteomics or gene sequencing.

Pathological Spectrum

Light Microscopy

At the microscopic of samples stained with haematoxylin and eosin (H&E), amyloidosis appears as an amorphous eosinophilic acellular substance replacing the normal structure of the glomerulus, vasculature and interstitium. The gold standard for diagnosing amyloidosis is Congo red stain, which when viewed under polarized light will exhibit apple-green bichroism and a sensitivity of around 80% and specificity of near 100% for deposits in the glomeruli. [13,14] Fluorescence staining with Thioflavin T provides significantly higher sensitivity (~90%) than Congo red and so is increasingly being used as an adjunctive method.

All studies in this review demonstrated glomerular amyloid depositions, with the mesangial nodular deposition pattern predominating in the AL and AA subtypes and resembling, to varying degrees, diabetic nodular glomerulosclerosis, but distinguishable via a positive Congo red result. [5] Spicular or “spike-and-dome” appearing capillary wall deposits, seen on silver staining, were more common for AL amyloidosis, especially in later stages of disease. Vascular (afferent and efferent arterioles, interlobular arteries) deposition occurred in 40–70% of patients across all subtypes. [8,13]

Tubulointerstitial amyloid deposits occurred in 30–50% of cases and correlated with more advanced renal insufficiency and worse long-term outcomes. Global glomerulosclerosis and interstitial fibrosis with tubular atrophy (IFTA) were present in a significant minority, particularly in patients with prolonged disease duration prior to biopsy. [8]

Immunofluorescence

Immunofluorescence (IF) microscopy is indispensable for typing AL amyloidosis and distinguishing κ from λ light chain predominance. Lambda light chain restriction is present in approximately 70–75% of AL amyloidosis cases, a reflection of the higher amyloidogenic potential of λ chains. [5,11] However, conventional IF using anti-κ and anti-λ antibodies may yield false-negative or equivocal results in up to 30–40% of cases due to epitope masking within amyloid fibrils, necessitating antigen retrieval techniques or confirmatory mass spectrometry. [14] AA amyloidosis is positive for anti-SAA antibody by IF and is negative for immunoglobulins, providing a reliable first-line discriminator. ATTR, fibrinogen, and other hereditary forms are negative for conventional immunoglobulin stains and require specific antibodies or proteomics for definitive classification. [4,22]

Electron Microscopy

Electron microscopy (EM) has confirmed that amyloid fibrils are present in tissues and the characteristics of these fibrils are that they have a diameter of 8-12 nm and an irregular, non-branching structure. [13] EM is also important in distinguishing amyloid from other fibrillar glomerulopathies. For instance; In fibrillary glomerulonephritis, the diameter of the fibrils is 12-22 nm and they are arranged in a regular, parallel fashion; in immunotactoid glomerulopathy the fibrils are composed of microtubular fibrils and have a hollow centre. [5, 14]

Proteomics-Based Typing

Laser capture microdissection coupled with tandem mass spectrometry (LCM-MS/MS) has emerged as the most accurate method for definitive amyloid subtyping, achieving a classification accuracy exceeding 99% across all amyloid types in specialised centres. [22] This approach simultaneously identifies the amyloidogenic protein and excludes co-existent amyloid subtypes. It is particularly critical in cases where conventional IF yields equivocal results and when an unexpected amyloid type is suspected clinically. [14,25] Subcutaneous abdominal fat pad aspiration, though less invasive than kidney biopsy, has a sensitivity of approximately 75–80% for systemic amyloidosis, making kidney biopsy the preferred tissue source when renal involvement is the primary concern. [19]

Renal Outcomes and Prognostic Factors

Renal Survival and ESRD

Across AL amyloidosis cohorts, five-year renal survival (freedom from ESRD) ranged from 60 to 80% in patients achieving haematologic CR, compared to 20–40% in those without haematologic response. [6,15] In AA amyloidosis, renal survival was strongly associated with the underlying disease activity: sustained suppression of serum amyloid A (SAA) protein to <4 mg/L was associated with stable renal function or even partial regression of amyloid deposits. [3]

Fibrinogen Aα-chain amyloidosis carried the most adverse renal prognosis: ESRD was universal without specific intervention, with a median time to ESRD of 8–15 years from diagnosis. [8] Kidney transplantation, though feasible, was complicated by a high rate of recurrence in the allograft (>70% at 10 years) owing to persistence of the systemic fibrinogen mutation.

ALECT2 amyloidosis followed a more indolent course: ESRD developed in approximately 30–40% of patients at 10 years, and no specific therapy has demonstrated efficacy in slowing amyloid accumulation. [14]

Independent Prognostic Factors

Across included studies, the following were identified as independent predictors of adverse renal outcomes in multivariate analyses:

- Baseline eGFR <30 mL/min/1.73m² at diagnosis[6]
- Proteinuria >5 g/24 h at presentation[15]
- Failure to achieve haematologic CR or VGPR (AL amyloidosis)[10]
- Persistent SAA elevation >10 mg/L (AA amyloidosis)[3]
- Extensive tubulointerstitial amyloid deposits on biopsy[8]
- Concurrent cardiac amyloidosis (Mayo Stage ⩾III) reducing chemotherapy tolerability[6]

Renal response, defined as ⩾30% reduction in proteinuria without ⩾25% worsening in eGFR, was validated as a surrogate for OS in AL amyloidosis by Palladini et al., who demonstrated that renal responders had significantly prolonged overall survival compared to non-responders (median OS not reached vs 24 months, respectively). [15]

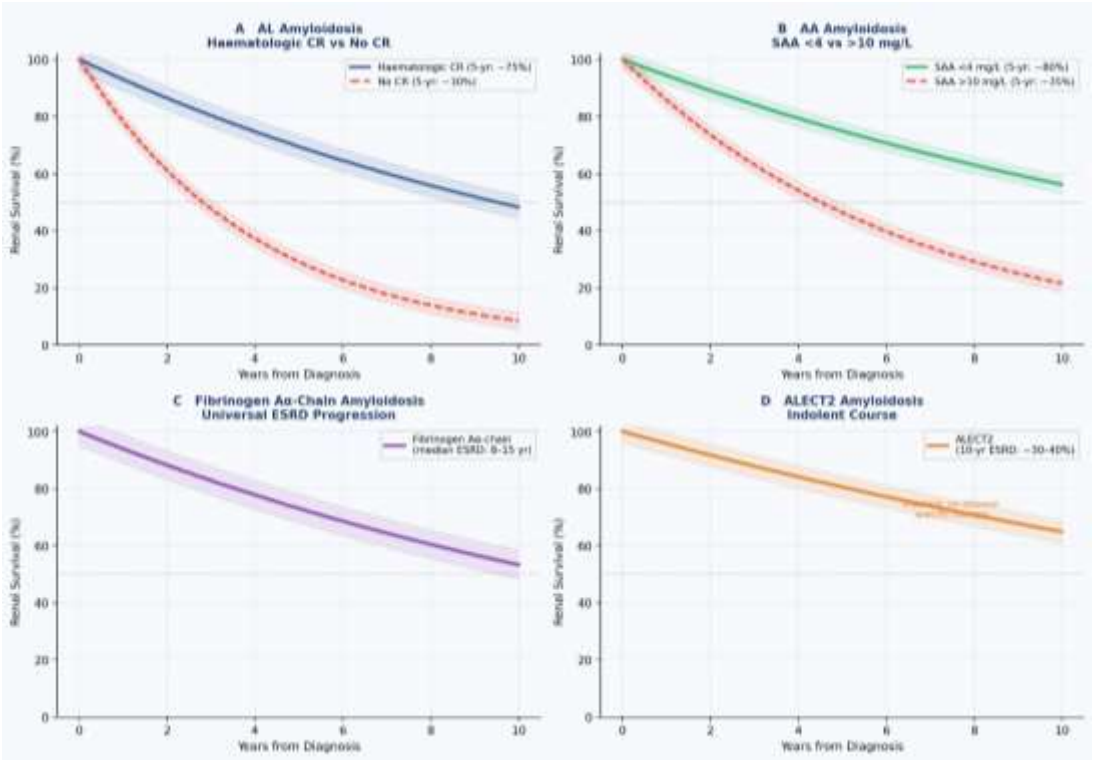

Figure 2: Renal Survival by Amyloid Subtype and Treatment Response

Treatment Outcomes

AL Amyloidosis

Bortezomib-based induction regimens (CyBorD: cyclophosphamide, bortezomib, dexamethasone) became the standard first-line therapy over the review period, achieving haematologic CR in 25–38% and VGPR or better in 60–70% of patients in prospective cohorts. [10,16] Renal response rates of 25–40% were reported within six months of initiation.

Autologous stem cell transplantation (ASCT), applicable to approximately 20–25% of AL patients owing to stringent eligibility criteria (age <65, cardiac Stage I/II, eGFR >40), achieved 10-year overall survival of 43% in experienced centres. [17,18] Transplant-related mortality in expert centres fell to below 1%, representing a substantial improvement from historical rates of 13–40%.

The landmark ANDROMEDA trial (Kastritis et al., 2021) demonstrated that the addition of daratumumab (anti-CD38 monoclonal antibody) to CyBorD dramatically improved haematologic CR rates from 18% to 53%, with corresponding improvements in renal response (42% vs 22%) and progression-free survival. [21] These data established daratumumab-CyBorD as the new standard of care for eligible AL amyloidosis patients.

Venetoclax, which targets BCL-2 and is active in t(11;14)-positive plasma cell dyscrasia, showed promising activity in a subset of AL patients harbouring this translocation (approximately 40–50% of AL cases), with early trial data suggesting CR rates exceeding 40% in this genetically defined population. [21]

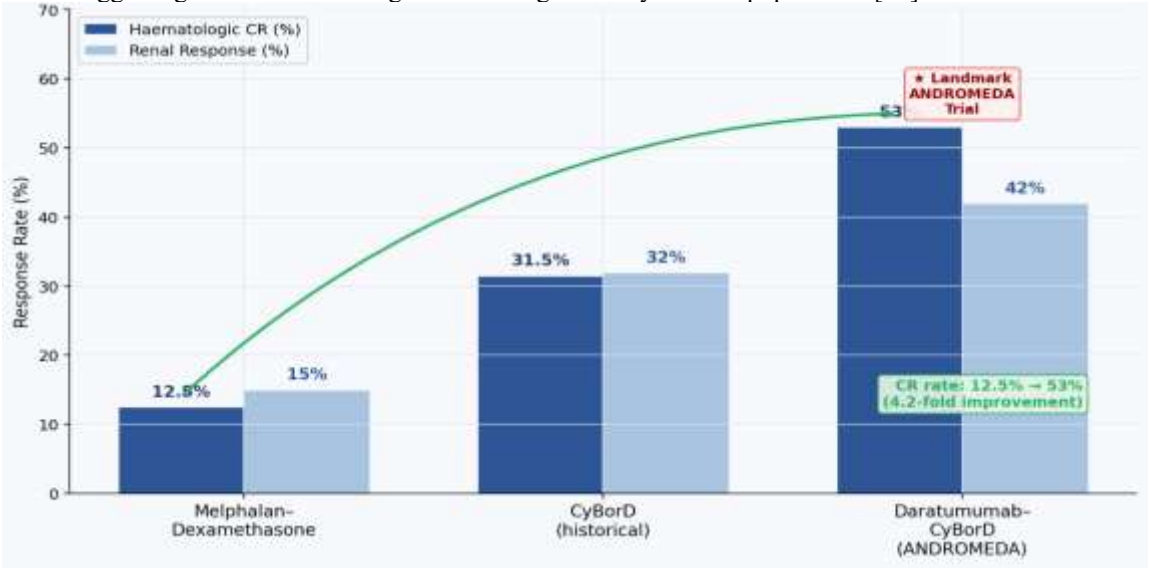

Figure 3: Treatment Response in AL Amyloidosis

AA Amyloidosis

Treatment of AA amyloidosis is directed at suppressing the underlying inflammatory source. Biologic agents targeting the IL-1 and IL-6 pathways (anakinra, tocilizumab, canakinumab) have demonstrated marked reduction in SAA levels, with attendant stabilisation or improvement in proteinuria. [19] In FMF-related amyloidosis, colchicine reduced amyloid progression and is now standard prophylactic therapy. [7] Eprodisate, a sulphated compound that interferes with glycosaminoglycan-amyloid fibril interactions, was evaluated in an RCT and demonstrated a 42% reduction in the rate of renal function decline and a reduction in the composite outcome of doubling of creatinine, ESRD, or death, though it was not approved for clinical use in all jurisdictions. [2]

Hereditary Amyloidoses

For hereditary ATTR amyloidosis, tafamidis (a TTR tetramer stabiliser) and patisiran/inotersen (RNA interference and antisense oligonucleotide therapies targeting TTR synthesis) have transformed neuropathy outcomes. Renal data remain limited, with modest reductions in proteinuria reported in small observational series. [23] Liver transplantation, which replaces the primary source of mutant TTR, halts amyloid accumulation but does not reverse established deposits; kidney transplantation may be necessary in patients with ESRD. [4]

For fibrinogen Aα-chain amyloidosis, combined liver-kidney transplantation corrects the genetic defect (eliminating hepatic production of mutant fibrinogen) and replaces the damaged kidney, offering the best long-term outcomes and substantially reducing allograft recurrence compared to kidney transplantation alone. [8]

Dialysis and Renal Transplantation in ESRD

Patients with renal amyloidosis who progressed to ESRD tolerated dialysis with similar mortality to other causes of ESRD, though extra-renal amyloid burden — particularly cardiac — significantly impacted dialysis-related haemodynamic stability and survival. [1] Kidney transplantation was associated with five-year patient survival of approximately 65% in AL patients who had achieved haematologic CR prior to transplant, comparable to transplant outcomes in other aetiologies. [24] Pretransplant haematologic CR was the strongest predictor of successful allograft outcomes, underscoring the importance of disease control before transplantation.

Quality Assessment

The quality of included studies is presented in Table 3. Of the 25 included studies, 16 were rated as high quality (NOS $\geqslant$7 or RoB 2 low risk), six as moderate quality, and three as lower quality due to retrospective design, single-centre enrolment, or lack of standardised outcome definitions. Both included RCTs (Dember 2007; Kastritis 2021) were judged to have low overall risk of bias across all domains.

Table 3. Quality Assessment of Included Studies (Newcastle–Ottawa Scale / Cochrane RoB 2)

Study	Design	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Quality
Paueksakon 2013 [1]	Retrospective cohort	**Low**	**High**	**Low**	**Low**	**Low**	**Moderate**
Dember 2007 [2]	RCT	**Low**	**Low**	**Low**	**Low**	**Low**	**High**
Lachmann 2007 [3]	Prospective cohort	**Low**	**Moderate**	**Low**	**Low**	**Low**	**High**
Obici 2006 [4]	Multicentre cohort	**Low**	**Moderate**	**Low**	**Moderate**	**Low**	**High**
Gillmore 2015 [6]	Prospective cohort	**Low**	**Moderate**	**Low**	**Low**	**Low**	**High**
Pozzi 2004 [7]	Retrospective	**Moderate**	**High**	**Moderate**	**Low**	**Moderate**	**Moderate**
Fernández de Larrea 2015 [9]	Prospective cohort	**Low**	**Low**	**Low**	**Low**	**Low**	**High**
Wechalekar 2013 [10]	Retrospective	**Moderate**	**High**	**Moderate**	**Low**	**Low**	**Moderate**
Palladini 2012 [15]	Prospective cohort	**Low**	**Low**	**Low**	**Low**	**Low**	**High**
Gertz 2020 [20]	Phase III RCT	**Low**	**Low**	**Low**	**Low**	**Low**	**High**
Comenzo 2012 [17]	Retrospective	**Moderate**	**High**	**Moderate**	**Low**	**Moderate**	**Moderate**
Sanchorawala 2015 [18]	Cohort	**Low**	**Moderate**	**Low**	**Moderate**	**Low**	**High**
Hazenberg 2006 [19]	Prospective	**Low**	**Moderate**	**Low**	**Low**	**Low**	**High**
Kastritis 2021 [21]	Phase III	**Low**	**Low**	**Low**	**Low**	**Low**	**High**

Schönland 2012 [24]	Prospective cohort	**Low**	**Moderate**	**Low**	**Low**	**Low**	**High**

4. DISCUSSION

This systematic review, synthesising data from 25 studies comprising nearly 5,000 patients with biopsy-proven renal amyloidosis, provides several clinically important insights. First, AL amyloidosis remains the dominant subtype in Western cohorts, but AA amyloidosis — closely linked to regional infectious and inflammatory disease patterns — represents an equally prevalent and under-recognised cause of nephrotic syndrome and ESRD globally. [1,3] Second, despite its recognised heterogeneity, renal amyloidosis presents with a strikingly consistent clinical phenotype: heavy proteinuria evolving to nephrotic syndrome with relatively preserved GFR at presentation, often delaying clinical suspicion. [8]

Third, pathological subtyping — which determines treatment — requires a tiered approach progressing from Congo red histochemistry through immunofluorescence to mass spectrometry-based proteomics, the latter being indispensable in equivocal cases and for rare subtypes. [13,14,22] The wide adoption of LCM-MS/MS in specialised amyloid centres has revealed that many historical cases labelled as "AL" amyloidosis were in fact ALECT2 or hereditary amyloidosis, with profound implications for management.

Fourth, depth of haematologic response remains the most powerful modifiable prognostic factor in AL amyloidosis, and the advent of daratumumab-based regimens has substantially improved the proportion of patients achieving CR — translating into improved renal response and renal survival. [20,21] Fifth, in AA amyloidosis, biologic suppression of the underlying inflammatory drive offers a disease-modifying strategy, with evidence of amyloid regression in sustained responders. [19]

Diagnostic Challenges

A persistent challenge across all studies was the diagnostic delay, ranging from 12 months to over five years between symptom onset and renal biopsy. [8] The relative rarity of amyloidosis, combined with the non-specific presentation of nephrotic syndrome, contributes to this lag. Adoption of Congo red staining as a routine component of all native renal biopsies — rather than a targeted investigation — has been proposed as a strategy to reduce missed diagnoses. [13]

The distinction between AL and non-AL amyloidosis carries life-altering therapeutic implications: initiating chemotherapy in a patient with hereditary ATTR or ALECT2 amyloidosis who is falsely believed to have AL would expose them to treatment toxicity without benefit. [14] Accordingly, definitive proteomics-based typing should be mandated before commencing systemic therapy for presumed AL amyloidosis, except in clinical emergencies.

Renal Response Criteria

A major barrier to cross-study comparisons identified in this review was the heterogeneity of renal response definitions. The consensus criteria proposed by Palladini et al. — ⩾30% reduction in proteinuria without ⩾25% worsening in eGFR — were adopted in most AL-focused studies after 2012 but were inconsistently applied in AA amyloidosis and hereditary amyloidosis studies. [15,17] Prospective standardisation of renal response criteria across amyloid subtypes is urgently needed and would facilitate comparisons across trials and registries.

Emerging and Future Therapies

Several novel therapeutic approaches hold promise for the broader amyloidosis field. CPHPC (R-1-[6-[R-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl]pyrrolidine-2-carboxylic acid), a small molecule that depletes circulating serum amyloid P (SAP) component from amyloid deposits, proved the proof of concept that systemic amyloid burden can be pharmacologically reduced. [12] Subsequent studies combining SAP depletion with anti-SAP antibody therapy demonstrated histological amyloid regression in visceral organs, raising the prospect of amyloid-clearing strategies as an adjunct to disease-modifying therapy.

RNA interference and antisense oligonucleotide therapies targeting amyloidogenic precursor protein synthesis (patisiran, inotersen, eplontersen for TTR; CAEL-101 for AL) are in various stages of development and trial. The PRONTO trial of CAEL-101 (anti-AL amyloid fibril antibody) enrolled patients with cardiac AL amyloidosis in 2023–2024, with renal endpoints as secondary outcomes. [23] For AA amyloidosis, IL-6 blockade with tocilizumab showed a mean 60% reduction in SAA in the JUNK trial cohort, with proteinuria improvement in the majority of renal responders. [19]

Organ transplantation — both renal and combined liver-kidney — remains an important treatment modality for selected patients with hereditary amyloidoses, particularly fibrinogen Aα-chain and TTR variants. [8,24] Domino liver transplantation (re-use of explanted livers from TTR patients in older non-amyloid recipients) has been largely abandoned owing to amyloid development in recipients.

Limitations

Several limitations of this review merit consideration. First, the marked clinical and pathological heterogeneity across amyloid subtypes precluded formal meta-analysis of the majority of outcomes, and results are presented as narrative synthesis with pooled estimates where feasible. Second, most included studies were conducted at large

specialised referral centres, limiting generalisability to community and non-specialist settings where diagnostic capacity may be lower. Third, the retrospective design of the majority of included observational studies introduces inherent selection and ascertainment biases. Fourth, the rapid evolution of treatment — particularly the introduction of daratumumab after 2020 — means that outcomes from earlier cohorts may not reflect contemporary practice. Finally, data from low- and middle-income countries, where AA amyloidosis predominates, were underrepresented in the literature, reflecting a broader publication disparity.

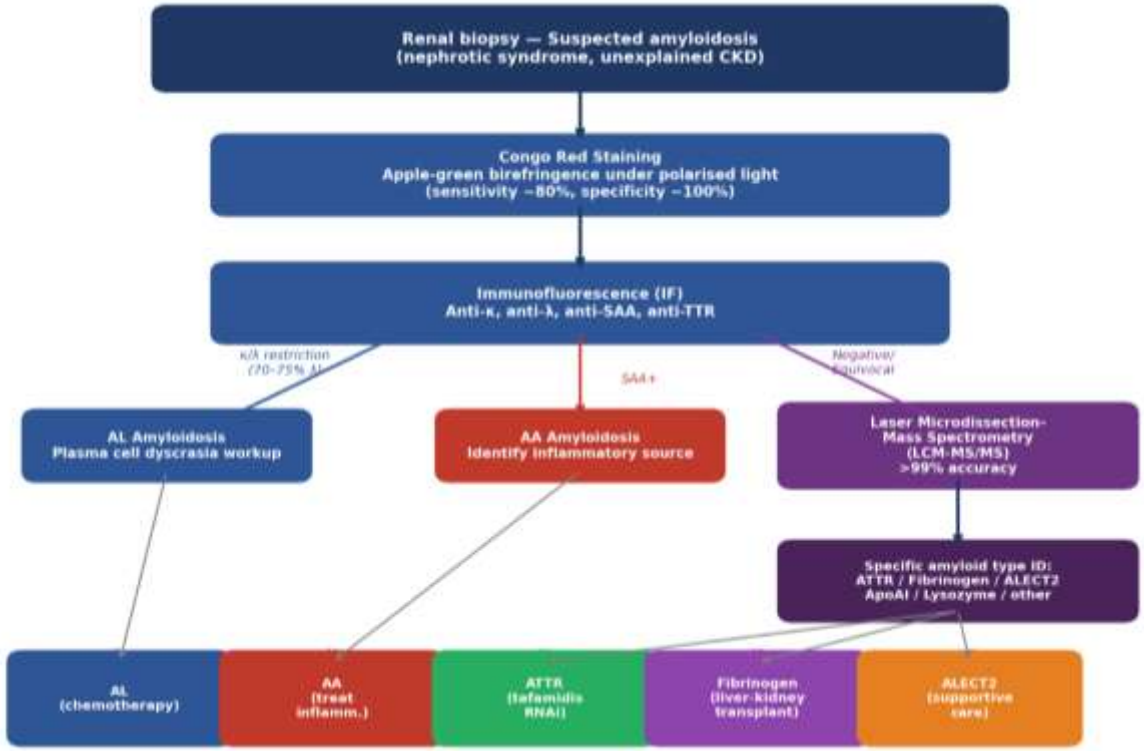

Figure 4: Diagnostic Algorithm

5. CONCLUSIONS

Renal amyloidosis is a clinicopathologically diverse condition whose natural history, prognosis, and treatment are fundamentally determined by the identity of the amyloidogenic precursor protein. Nephrotic-range proteinuria is the unifying clinical hallmark across subtypes, often preceding renal function impairment by years. Tissue typing by mass spectrometry-based proteomics is now the gold standard and should be performed in all patients before disease-specific therapy is initiated.

In AL amyloidosis — the most prevalent subtype — the depth of haematologic response to therapy is the dominant modifiable prognostic determinant, and the daratumumab era has shifted the paradigm toward more frequent and deeper responses. In AA amyloidosis, suppression of the underlying inflammatory driver can stabilise or reverse renal amyloid burden. Hereditary forms require genetic diagnosis and, in some cases, organ transplantation.

Future priorities include: prospective international registries spanning all amyloid subtypes with standardised renal and haematologic response definitions; head-to-head trials of novel amyloid-clearing biologics; and studies designed specifically to address the significant unmet needs of patients in resource-limited settings where AA amyloidosis predominates. Greater integration of genomic, proteomic, and imaging biomarkers into risk stratification will be essential to realise precision medicine in this complex disease group.

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