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Research Article

Correlations of Minimal Residual Disease Status with Hematologic Progression, Organ Response and Survival in Systemic AL Amyloidosis Patients Who Achieved Complete or Very Good Partial Hematologic Response: Updated Systematic Literature Review

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Abstract

Systemic light chain (AL) amyloidosis is a rare, clonal plasma cell disorder that is characterized by extracellular deposition of amyloid fibrils within various organs which leads to significant organ dysfunction and ultimate death if left untreated. Current treatment strategies aim to reduce amyloid fibril production by clonal plasma cells. Despite achieving hematologic complete response (CR) or very good partial response (VGPR) with treatments, many patients relapse or continue to have organ dysfunction. Current studies highlight a direct correlation between depth of hematologic response with favorable survival outcomes, therefore detection and monitoring of very low levels of amyloidogenic clonal plasma cells can potentially impact survival. Minimal residual disease (MRD) is defined as detection of clonal plasma cells within a sample size of bone marrow cells ranging from 10,000(10^{-4}) to 1,000,000 (10^{-6}) cells. This systematic review aims to analyze the evidence regarding correlations between MRD negativity and hematologic progression, organ response, and survival outcomes in systemic AL amyloidosis patients who have achieved CR or VGPR. A total of 13 studies published between January 2015, and May 2025 were included after screening PubMed/MEDLINE, Embase, Cochrane Library with predefined eligibility criteria. Patients with negative MRD showed lower hematologic progression rates, better cardiac and renal organ responses and improved progression free survival. Most studies in this review utilized multiparameter flow cytometry (MFC) at ≥10^{-5} sensitivity to assess MRD, but methodologies were heterogenous across the studies. In conclusion, MRD negativity is a potential independent prognostic biomarker in systemic AL amyloidosis, but large-scale, multi-centered, prospective studies with uniform, standardized MRD assessment methods are needed to validate it as a surrogate for survival.

Introduction

Systemic light chain (AL) amyloidosis is a rare, clonal plasma cell disorder that is characterized by extracellular deposition of amyloid fibrils within various organs [1]. Amyloid fibrils form due to misfolding of monoclonal immunoglobulin light chain proteins produced by malignant clonal plasma cells. Amyloid fibril deposition in tissues often leads to progressive and eventually fatal organ damage. Renal involvement occurs in nearly 70% of cases, leading to proteinuria, and progressive chronic kidney disease [2]. Cardiac amyloidosis manifests as restrictive cardiomyopathy, diastolic dysfunction, or arrhythmias. Severity of cardiac disease predicts survival, with advanced cases showing very poor outcomes [3]. Other sites, including liver, gastrointestinal tract, and nerves, may also be affected, complicating diagnosis and management [4]. Early diagnosis, timely initiation of effective treatments, and standardized monitoring strategies constitute critical determinants of prognosis. Current frontline treatments target clonal plasma cells to reduce amyloidogenic light chain production. Alkylating agents such as melphalan, proteasome inhibitors like bortezomib, and immunomodulatory drugs have been reported to improve outcomes [1,5]. Autologous stem cell transplantation (ASCT) after high dose melphalan conditioning also offers long-term survival and high organ response in selected patients [6]. Combination regimen daratumumab, cyclophosphamide, bortezomib, and dexamethasone (DaraCyBorD) is now the standard of care, with high response rates and improved survival (ANROMEDA trial) [7]. Newer treatment approaches that are currently under investigation for systemic AL amyloidosis include immunotherapy based treatments such as monoclonal antibodies CAEL 101 or birtamimab which bind to already deposited amyloid fibrils in tissues triggering an immune response [8], antibody drug conjugates such as belantamab mafodotin, bispecific antibodies (BSA) and chimeric antigen receptor (CAR) T cell therapy directed against malignant plasma cells [1,9,10]. Frontline treatments aim to achieve hematologic complete response (CR) or very good partial response (VGPR). CR is defined as absence of monoclonal protein

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in serum and urine by immunofixation assays and normalization of serum free light chain (FLC) ratio. VGPR is defined as <40 mg/L difference between involved and uninvolved FLCs. CR correlates with improved survival and organ recovery [4]. However, despite achieving hematologic CR, many patients with AL amyloidosis continue to have organ dysfunction or develop hematologic progression over time. The reasons for this phenomenon suggested to be due to persistence of already deposited amyloid fibrils, irreversible organ damage and circulation of very low levels of amyloidogenic light chains produced by treatment resistant residual plasma cells that are undetected with conventional immunofixation assays [11,12]. Depth of hematologic response independently correlates with favorable survival outcomes [11], therefore detection and monitoring of very low levels of abnormal clonal plasma cells can potentially impact survival. In the last decade, the concept of minimal residual disease (MRD) which is defined as detection of clonal plasma cells within a sample size of bone marrow cells ranging from 10,000 (10^{-4}) to 1,000,000 (10^{-6}) cells has emerged in multiple myeloma as a prognostic factor that predicts clinical and survival outcomes [13,14,15]. However, the significance of MRD in systemic AL amyloidosis remains less explicit given studies on this topic mostly consist of retrospective studies with small number of patients. In majority of published literature on this topic and in this systematic review, the term "MRD negative" is used for undetectable MRD and "MRD positive" is used for detectable MRD.

Evidence from retrospective studies links MRD negativity to improved organ response and progression free survival (PFS) in systematic AL amyloidosis. A recent meta-analysis [16] correlated MRD negativity with higher cardiac and renal response rates [pooled risk ratio (RR) = 0.74 (95% CI 0.62-0.89), 0.74 (95% CI 0.64-0.87), respectively]. Patients with MRD positivity had a higher hematologic progression rate within two years after MRD detection [pooled RR = 10.31 (95% CI 2.02-52.68)]. Moreover, MRD negativity was correlated with a better PFS [pooled hazard ratio (HR) = 0.27 (95% CI 0.17-0.45)]; but it did not significantly improve the overall survival (OS) [pooled HR = 0.34 (95% CI 0.11-1.07)].

MRD negativity is now considered a meaningful endpoint alongside CR, refining prognostic evaluation, however standardization of techniques for MRD detection remains a challenge. Lack of uniform definitions hinders comparability [17]. Unlike multiple myeloma, MRD negativity is not yet a validated endpoint or surrogate marker in AL amyloidosis [18]. Debate continues whether MRD should guide treatment decisions [19] or not in AL amyloidosis. Large, multi-centered trials are needed to establish clinical utility. Advances such as ultra-sensitive methods [20,21], International Myeloma Working Group (IMWG) and European Consortium (EuroFlow) standardization [22], and integration into clinical trials [23] support progress. Still, heterogeneity and limited pooled data restrict guideline development [16,22]. This systematic review will highlight the current evidence in literature on MRD status and its correlations with hematologic progression, organ response, and survival in systemic AL amyloidosis patients who achieved CR or VGPR. Objectives include summarizing MRD methodologies, analyzing correlations of MRD status with hematologic progression, organ response, survival outcomes, and identifying research gaps. The overall aim is to support integration of MRD detection into practice and research as a standardized prognostic biomarker.

Methods

PRISMA Statement

This systematic review was conducted following the guidelines provided in the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA 2020) updated statement which facilitates transparent and complete reporting of systematic reviews [24]. The methodological framework had been established before the search of databases and included the definition of eligibility criteria, the sources of data, the search strategy, the study selection procedures, and data extraction procedures.

Search Strategy

The search was conducted in electronic databases of PubMed/MEDLINE, Embase, Cochrane Library. The searches were limited between January 2015 and May 2025 in time.

The finalized PubMed/Embase search strategy was as follows: ("AL amyloidosis*" OR "Light chain amyloidosis*" OR "Immunoglobulin amyloidosis*" OR "Primary amyloidosis*") AND ("Minimal residual disease*" OR "MRD" OR "Residual neoplasm*" OR "Residual disease*" OR "Measurable residual disease*") AND ("Response*" OR "Relapse*" OR "Organ response*" OR "Survived*" OR "Overall survival*" OR "Progression*" OR "Progression free survival*" (Figure 1). Equivalent Boolean strategies with both medical subject headings (MeSH) terms and free-text keywords were adapted for other databases. Only English-language studies were retained for final analysis to ensure consistency in interpretation.

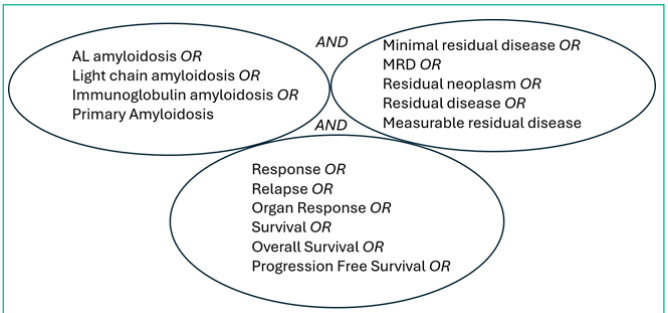

Figure 1: chromatogram of sample solution (80 µg/mL).

Eligibility Criteria

Inclusion Criteria:

Studies were eligible if they met the following requirements:

1. Population: Adults (≥18 years) with biopsy proven systemic AL amyloidosis.

Intervention/Exposure: Patients who achieved hematologic CR, as defined by consensus criteria (absence of monoclonal protein is serum and urine by immunofixation and normalization of serum free light chain ratios) or hematologic very good partial response (VGPR) defined as reduction in the difference between the involved and uninvolved serum free light chains (dFLC) to < 40 mg/L [25].

2. Comparator: MRD-positive vs. MRD-negative status, MRD detectable vs MRD undetectable

3. Outcomes: At least one of the following:

- Hematologic progression.
- Organ response (renal, cardiac).
- Survival outcomes, including overall survival (OS) or progression free survival (PFS).

4. Study Design: Randomized controlled trials, prospective or retrospective observational studies, and cohort studies with original MRD outcome data or substantive methodological insights.

Exclusion Criteria:

1. Studies on non-AL type amyloidosis.
2. Studies not reporting MRD status or not reporting correlations of MRD with clinical outcomes.
3. Preclinical animal or in vitro studies.
4. Non-English language publications where translations were unavailable.

Study Selection Process

The initial database search identified 36 potentially relevant records. After removal of duplicates, titles and abstracts were screened and full texts of potentially eligible studies were then assessed.

At this stage, studies were excluded if:

- They did not include systemic AL amyloidosis patients (e.g., studies restricted to multiple myeloma).
- They were narrative reviews without original patient outcome data.
- They were meta-analysis consisting of studies that were already included
- They were poster or oral presentations in conferences
- The full text was not retrievable despite reasonable efforts.

Following this screening, 13 studies met the eligibility criteria (Figure 2).

Data Extraction

Data included bibliographic details (authors, year) and study characteristics (design, country, sample size). Patient demographics including median age, age range, sex/gender, organ involvement, and disease stage collected. MRD detection techniques and sensitivity thresholds were recorded, including detection by multiparametric flow cytometry (MFC), next generation flow cytometry (NGF), next generation sequencing (NGS), and mass spectrometry (MS). Timing of MRD assessment also recorded if this information was available. Response definitions were based on validated consensus criteria, including CR, VGPR, cardiac and renal responses [25]. Given heart and kidney are the main organs that impact survival for majority of AL amyloidosis patients, data on other organ responses such as hepatic response not included in this review. Outcomes included hematologic progression rates, organ response, PFS and OS. Data on median follow-up length was extracted. During data extraction artificial intelligence research assistant tool "Elicit" utilized in addition to manual data extraction.

Results

Summary of Included Studies

This review included 13 studies with total 1053 patients with systemic AL amyloidosis who underwent MRD assessment. Details of the studies are shown at Table 1. Studies were from United Stated of America (Chakraborty et al., 2022; [12,26-28]), United Kingdom [29], China [30,31], Greece [32], Canada (Diaz-Pallares et al., 2020) and multinational collaborations [33,34]. Eight of the studies were retrospective cohorts, five were prospective observational studies (one clinical trial and one pilot study). Patient characteristics are summarized at Table 2. Age range of total patients in 13 studies was 30-88 years. Male patients were more frequent with overall range

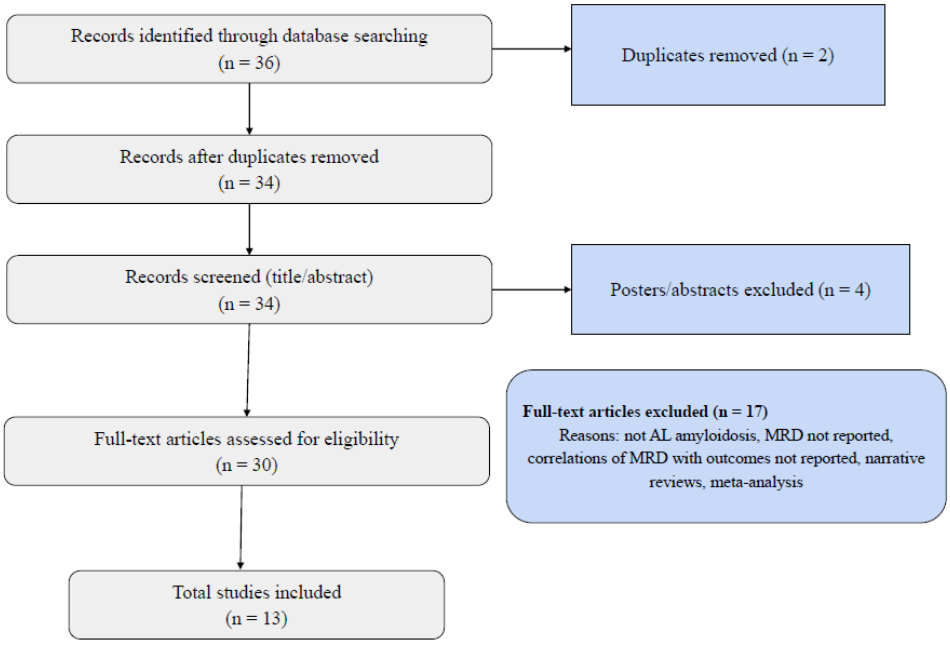

Figure 2: Flowchart describing study inclusion process.

Table 1: Study Characteristics.

Reference	Study Period	Country	Study Design	Sample Size (n)
Bomsztyk et. al, 2020	Not reported	UK	Prospective	487
Chakraborty et al., 2022	05/2016-12/2019	USA	Retrospective	45
Diaz-Pallares et al., 2020	01/2012-08/2018	Canada	Retrospective	34
Dispenzieri et al., 2020	01/2000-05/2005	USA	Retrospective	33
Kastritis et al., 2021	05/2016-12/2019	Greece	Prospective	51
Landau et al., 2020	06/2011-04/2019	USA	Prospective pilot study	19
Li et al., 2022	2012-07/2019	China	Retrospective	25
Muchtar et. al, 2020	02/2012-11/2015	USA	Retrospective	82
Palladini et al., 2021	04/2016-07/2019	Italy, Spain, UK	Prospective	92
Sarosiek et al., 2021	11/2016-07/2019	USA	Prospective clinical trial (NCT02716103)	13
Sidana et al., 2020	08/2017-11/2018	USA, Australia	Retrospective	44
Staron et al., 2020	02/2019-11/2019	USA	Retrospective	65
Xu et al., 2024	01/2016-2023	China	Retrospective	63

Abbreviations: UK (United Kingdom), USA (United States of America), n(number), NCT (national clinical trial).

40-72%, and weighted average 59%. Median follow up ranged from 14 months to 4.6 years (Table 3). Cardiac and renal involvements were the most analyzed organ responses. Most patients had either hematologic CR or VGPR at the time of MRD assessment (Table 2). The most common MRD detection method used was MFC with $\geq 10^{-5}$ sensitivity. Other methods were NGF, NGS and MS. Timing of MRD assessment was heterogeneous across the studies (Table 3).

Correlation of MRD with Hematologic Progression

Out of 13 studies included in this systematic review, only 5 studies reported correlations with MRD status and hematologic disease progression [26,30,32,33,34] (Table 4). All these 5 studies showed less frequency of hematologic progression in MRD negative subgroups (Table 4) with some reporting statistical significance (Dispenzieri et al. p=0.003; Kastritis et al. p=0.029; Palladini et al. p=0.001). Dispenzieri et al. evaluated 33 patients with AL amyloidosis who achieved CR and had negative bone marrow for clonal plasma cells by six-color flow cytometry. Serum and urine samples of these patients were screened with matrix-assisted laser desorption/ionization-time-of-flight (TOF) mass spectrometry (MASS-FIX) and further analyzed with electrospray ionization and quadrupole TOF mass spectrometry (ESI-TOF). Four out of 33 CR patients were observed to have residual disease with detection of monoclonal free light chains (FLC) with mass spectrometry. By 50 months of follow-up, 75% of patients with positive mass spectrometry had hematologic progression events in contrast to 13% in the mass spectrometry-negative group, (p = 0.003).

Kastritis et al. studied NGF to detect MRD in 51 AL amyloidosis patients with CR and found that at a median sensitivity of 2.3×10^{-6}, MRD was negative in 45% of patients. After a median follow-up of 24 months post MRD assessments, no patients with negative MRD had a hematologic progression compared to 21% of positive MRD patients (p = 0.029).

Palladini et al. evaluated 92 patients with AL amyloidosis in CR for MRD status by NGF (with minimum sensitivity of 10^{-5} in all patients

Table 2: Patient Characteristics.

Reference	Age median, (range)	Male %	No. of Total Patients	No. CR/VGPR patients (%)
Bomsztyk et. al, 2020	67 (36-88)	59.60%	487	126 (26)
Chakraborty et al., 2022	66 (39-78)	Not reported	45	38 (84)
Diaz-Pallares et al., 2020	64 (not reported)	58.80%	34	18 (53)
Dispenzieri et al., 2020	56 (44, 81)	55%	33	33 (100)
Kastritis et al., 2021	62 (42–77)	52%	51	23 (45)
Landau et al., 2020	60 (38-73)	68%	19	14 (73.7)
Li et al., 2022	59 (42-80)	40%	25	25 (100)
Muchtar et. al, 2020	61 (43–77)	68%	82	54 (66)
Palladini et al., 2021	MRD negative: 61 (55–68) MRD positive: 59 (55–66)	58.70%	92	92 (100)
Sarosiek et al., 2021	Not reported	Not reported	13	12 (92)
Sidana et al., 2020	63 (58–69)	59%	44	42 (95)
Staron et al., 2020	MRD negative: 60 (32-76) MRD positive: 61 (30-74)	MRD negative: 52% MRD positive: 72%	65	65 (100)
Xu et al., 2024	60(54-66)	58%	63	45 (71)

Abbreviations: No. (number), CR (complete response), VGPR (very good partial response), MRD (minimal residual disease).

Table 3: Details of MRD Assessments.

Reference	MRD detection method	Sensitivity of MRD Assay	Median Follow-Up	Timing of MRD Assessment
Bomsztyk et. al, 2020	FLC-MS (MALDI-TOF)	Not applicable	Not reported	6 months and 12 months after treatment
Chakraborty et al., 2022	MFC	$\geq 10^{-5}$	22.5 months	Within 1.5 years of treatment initiation
Diaz-Pallares et al., 2020	MFC	10^{-4}	24 months	After median 4 cycles
Dispenzieri et al., 2020	MASS-FIX, ESI-TOF	Not applicable	116 months	Median 18 months after treatment
Kastritis et al., 2021	NGF-MFC	3.1×10^{-6} to 2x 10^{-6}	24 months	Median 6 months (range 3-12 months) after achieving CR
Landau et al., 2020	MFC	Up to 10^{-6}	61 months	Before ASCT, 12 and 24 months after ASCT
Li et al., 2022	MFC	5×10^{-5} to 10^{-5} cells	25.1 months	3 months arter first line treatment
Muchtar et. al, 2020	MFC	1×10^{-4} to 2×10^{-5}	4.6 years	At the end of treatment
Palladini et al., 2021	NGF -MFC	$\geq 10^{-5}$	23 months	At least 6 months after treatment
Sarosiek et al., 2021	NGS (ClonoSeq)	$\geq 10^{-6}$	Not reported	Prior to treatment and at median of 447 days (range, 147-918) after treatment
Sidana et al., 2020	NGF	$\geq 10^{-5}$	14 months	Within 2 years of treatment initiation (median 7 months)
Staron et al., 2020	MFC	$\geq 10^{-5}$	Not reported	Median 72 months after achieving CR for MRD negative patients, median 32 months after achieveing CR for MRD positive patients
Xu et al., 2024	NGF	$\geq 10^{-5}$	27.2 months	Every 2 cycles during treatment

Abbreviations: MRD (minimal residual disease), FLC-MS (free light chain mass spectrometry), MALDI-TOF (matrix-assisted laser desorption/ionization-time-of-flight mass spectrometry), MFC (multiparameter flow cytometry), MASS-FIX (matrix-assisted laser desorption ionization time-of-flight mass spectrometry), ESI-TOFI (electrospray ionization time-of-flight mass spectrometry), NGF (next generation flow cytometry), NGS (next generation sequencing), CR (complete response), ASCT (autologous stem cell transplant).

Table 4: Comparison of Clinical Outcomes for MRD negative vs. MRD positive Patients.

Reference		MRD negative	MRD positive	p- value
Bomsztyk et. al, 2020				
Comparison for 12 month FLC-MS (-) vs FLC-MS (+)	Cardiac Response	19.60%	9%	**0.0162**
	Renal Response	38%	not reported	**0.015**
	Disease Progression	not reported	not reported	
	Survival	Median OS not reached	108 months	**0.024**
Chakraborty et al., 2022				
Comparison at follow-up	Cardiac Response	92%	71%	0.18
	Renal Response	60%	79%	0.33
	Disease Progression	not reported	not reported	
	Survival	mMOD-PFS not reached	55 months	0.28
Diaz-Pallares et al., 2020				
	Cardiac Response	not reported	not reported	
	Renal Response	not reported	not reported	
	Disease Progression	not reported	not reported	
	Survival	OS/PFS not significantly different	OS/PFS not significantly different	> 0.05
Dispenzieri et al., 2020				
	Cardiac Response	not reported	not reported	
	Renal Response	not reported	not reported	
	Disease Progression	13% by 50 months	75% at by 50 months	**0.003**
	Survival	83% at 10 years	62% at 10 years	> 0.05
Kastritis et al., 2021				
	Cardiac Response	100%	73%	
	Renal Response	88%	87.50%	
	Disease Progression	Organ 4%, Hematologic 0%	Organ 21%, Hematologic 21%	Organ 0.094, Hematologic **0.029**
	Survival	PFS 96%	PFS 68%	**0.026**
Landau et al., 2020				
	Cardiac Response	not reported	not reported	
	Renal Response	not reported	not reported	
	Disease Progression	0%	not reported	
	Survival	PFS superior at 1 year	not reported	**0.008**
Li et al., 2022				
	Cardiac Response	93%	25%	**0.019**
	Renal Response	50%	82%	0.116
	Disease Progression	Hematologic or Organ 11.8%	Hematologic or Organ 62.5%	
	Survival	PFS 76.39 months	PFS 24.52 months	PFS **0.004**, OS 0.2
Muchtar et. al, 2020				
	Cardiac Response	100%	83%	0.13
	Renal Response	100%	68%	**0.005**
	Disease Progression	not reported	not reported	
	Survival	PFS 88%, OS 96% at 3 years	PFS 28%, OS 84% at 3 years	PFS **<0.001**, OS 0.17
Reference		**MRD negative**	**MRD positive**	**p- value**
Palladini et al., 2021				
	Cardiac Response	95%	75%	0.023
	Renal Response	90%	62%	**0.006**
	Disease Progression	Hematologic progression 2%	Hematologic progression 26%	**0.001**
	Survival	not reported	3 patients died at median 23 month	0.203
Sarosiek et al., 2021				
	Cardiac Response	not reported	60%	
	Renal Response	not reported	78%	
	Disease Progression	not reported	not reported	
	Survival	not reported	not reported	
Sidana et al., 2020				
	Cardiac Response	67% at MRD assesment; 64% at 1 year	22% at MRD asessment; 50% at 1 year	**0.04**; 0.6
	Renal Response	69% at MRD assessment, 81% at 1 year	89% atMRD assessment, 86% at 1 year	0.2; 0.8
	Disease Progression	Hematologic+Organ 0% at 1 year	Hematologic+Organ 36% at 1 year	
	Survival	PFS 100% at 1 year, no significant difference in OS	PFS 64% at 1 year, no significant difference in OS	PFS **0.006**

Staron et al., 2020				
	Cardiac Response	75%	59%	0.45
	Renal Response	88%	64%	0.06
	Disease Progression	not reported	not reported	
	Survival	not reported	not reported	
Xu et al., 2024				
	Cardiac Response	66.70%	38.10%	**0.032**
	Renal Response	not reported	not reported	
	Disease Progression	not reported	not reported	
	Survival	Median EFS not reached, Median PFS not reached, Median OS not reached	Median EFS 19.9 months, Median PFS 31.3 months, Median OS not reached	EFS **0.031,** PFS **0.033,** OS 0.786

Abbreviations: MRD (minimal residual disease), FLC-MS (free light chain mass spectrometry), PFS (progression free survival), OS (overall survival), mMOD-PFS (major organ deterioration-progression free survival), EFS (event free survival).

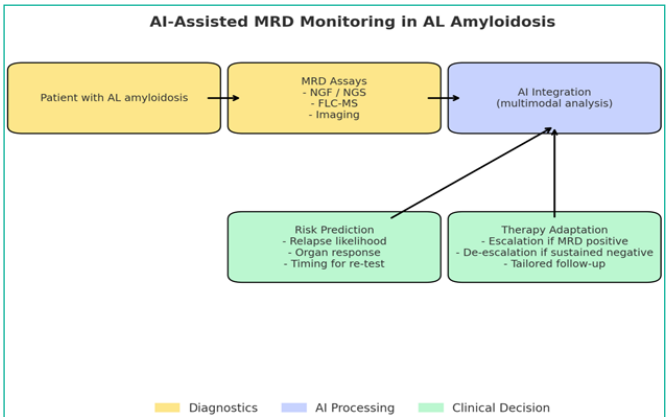

Figure 3: Workflow diagram of AI integration into MRD monitoring - figure generated with ChatGPT-5 pro.

and and 10^{-6} sensitivity in 76% patients), and observed that 54% of patients had positive MRD. Hematologic progression within median 23 months of follow-up since MRD asessment was significantly more frequent in MRD positive patients (2% vs 26%, $p = 0.001$).

Sidana et al. evaluated MRD detection using NGF with sensitivity $\geq 1 \times 10^{-5}$ in 44 patients with AL amyloidosis, and observed the overall rate of MRD positivity was 64%. At 1 year follow-up, 36% of MRD positive patients had combined hematologic and organ progression compared to 0% patients in MRD negative subgroup.

Correlation of MRD with Cardiac Response

Ten out of 13 studies included in this review compared cardiac response in MRD negative and positive patients (Table 4). Bomsztyk et al. [29] evaluated serum samples of 487 newly diagnosed AL amyloidosis patients enrolled in a prospective observational study in United Kingdom National Amyloidosis Center for monoclonal FLC detection with mass spectrometry (MS). A total of 290 patients (59.5%) had cardiac involvement at the time diagnosis, but only 237 patients had avaliable data for cardiac response at 12 months time period. Cardiac response rate was 19.6% in FLC-MS negative patients vs 9% in FLC-MS positive patients at 12 moths (p=0.0162).

Chakraborty et al. assessed MRD with MFC (sentivity $\geq 10^{-5}$) on 45 AL amyloidosis patients, and 26 of them had assessable data for cardiac organ response. Median follow-up was 22.5 months. At most recent follow-up after MRD assessment, the incidence of cardiac organ response in MRD negative vs positive patients were 92 % vs 71% (p= 0.18).

Kastritis et al. [32] showed cardiac response in 100% of MRD negative patients vs 73% of MRD positive patients during median follow-up of 24 months. Li et al. [30] evaluated 25 newly diagnosed AL amyloidosis patients with MFC (sensitivity 5×10^{-5}–10^{-5}) three months after first line treatment completion. MRD negative patients had 93% cardiac response rate compared to 25% MRD positive patients (p = 0.019).

Muchtar and et al. [28] evaluated 82 patients with AL amyloidosis with VPGR or above for MRD status at the end of treatment with MFC (sensitivity 1×10^{-4}–2×10^{-5}), but only 20 patients had available data for cardiac response. Out of these 20 patients with cardiac involvement, eight had MRD negative, 12 had MRD positive status. MRD negative patients achieved cardiac response at 100% rate compared to 83% in MRD positive patients (p=0.13).

Palladini et al. showed that the rate of cardiac response was 95% in MRD negative patients vs 75% in MRD positive patients (p = 0.023).

Sarosiek et al. [12] conducted a prospective study with 36 newly diagnosed AL amyloidosis patients, using the NGS (clonoSEQ Assay-Adaptive Biotechnologies Inc.,Seattle, WA) for clonal identification. 13 patients had post-treatment testing at a median follow-up of 447 days from initial testing, 5 out of 13 had cardiac involvement at baseline. Of those with cardiac involvement, 60% (3 out of 5) had cardiac response at the time of MRD assessment.

In Sidana et al.'s [33] study, 21 patients out of 44 had heart involvement. MRD negative patients were more likely to have achieved cardiac response at the time of MRD assessment compared to MRD positive patients (67% vs 22%, p =0.04). At one year, 64% of MRD negative patients had cardiac response while 50% of MRD positive patients had cardiac response (p=0.6).

Staron et al. [35] evaluated 65 AL amyloidosis patients for MRD status with MFC (sensitivity $\geq 10^{-5}$) at different time points after CR achievement. Heart involvement was seen in 17 patients. Cardiac response was achieved in 75% of MRD negative patients vs 59% of MRD positive patients (p= 0.45).

Xu et al. [31] evaluated MRD status in 63 cardiac AL amyloidosis patients with NGF (sensitivity $\geq 1\times10^{-5}$). All patients were treated with first-line proteasome inhibitor mostly with bortezomib (87.3%). MRD negativity was associated with a higher likelihood of cardiac response defined as 30% reduction in NT-proBNP from baseline throughout first-line therapy (66.7% vs 38.1% (p= 0.032) and within four cycles (61.9% vs 28.6% p= 0.011). MRD negativity was also associated with a higher likelihood of ≥ very good partial cardiac response (> 60%

reduction in NT-proBNP from baseline) throughout first-line therapy (38.1% vs 11.9% , p= 0.023).

Correlation of MRD with Renal Response

Nine studies in this review had data on renal response (Table 4). Bomsztyk et al. [29] reported 71.1% of patients (349/487) had renal involvement at diagnosis, with 303 and 313 patients had data for renal response assessment at 6 and 12 months, respectively. Renal response rate was 22.2% in 6 months and 26.2% in 12 months for all patients. Subgroup analysis showed that patients reaching FLC-MS negativity had 26% and 38% renal response rates at 6 and 12 months, respectively (p= 0.45 and p=0 .015) compared to patients with FLC-MS positivity.

Chakraborty et al. assessed a total of 24 patients for renal response. The renal response rate was 60% in MRD negative patients compared to 69% in MRD positive patients (p= 0.18) at most recent follow up. Although, MRD positive patients had higher rates of renal response, median time to reach best renal response was longer for MRD positive patients. The median time to best renal response was 18.3 months (IQR, 6.6–34.1), with the median duration being 23.0 months (IQR, 5.7–42.2) in MRD positive and 19.9 months (IQR, 12.6–31.1) in MRD negative patients. Kastritis et al. [32] showed that among those with kidney involvement, patients with negative MRD status had similar (88%) renal response rates compared to MRD positive patients (87.5%).

Muchtar et al. [28] had data on 33 patients who achieved VGPR or better hematologic response for evaluating correlation of MRD status with renal response. MRD negative patients showed 100% renal response rate compared to 68% response rate in MRD positive patients (p=0.005).

Li et al. [30] observed 50% renal response rate in MRD negative patients compared to 82% in MRD positive patients (p= 0.116).

Palladini et al. [34] reported that patients with negative MRD were more likely to achieve renal response (92%) compared to MRD positive patients (62%), p = 0.006.

Sarosiek et al. [12] observed 78% renal response rate at the time of MRD assessment in MRD positive patients.

Sidana et al. [33] observed that renal response rates were not significantly different between MRD negative (89%) and MRD positive (69%) patients, (p=0.2). Within one year of the MRD assessment, the renal response rates remained similar; 81% at MRD negative patients vs 86% at MRD positive patients vs (p=0.8).

Staron et al. [35] reported renal response rate of 88% in MRD negative patients vs 64% in MRD positive patients (p=0.06).

Correlation of MRD with Survival Outcomes

In this review, most of the studies that analyzed the survival outcomes in relation to MRD status pointed towards improved PFS for MRD negative patients (Table 4). PFS difference among MRD negative vs positive patients reached statistical significance in the studies of Kastiritis et al. [32] (PFS 96% in MRD negative vs 68% in MRD positive, p = 0.02), Li et al. (PFS 76.39 months in MRD negative, 24.52 months in MRD positive, p = 0.004), Muchtar et al. [28] (3 year PFS 88% in MRD negative vs 28 % in MRD positive p <0.001), Sidana et al. [33] (1 year PFS 100% in MRD negative vs 64% in MRD positive, p = 0.006), Xu et al. [31] Median event free survival (EFS) and PFS were not reached in MRD negative patients, median EFS was 19.9 months, median PFS was 31.3 months in MRD positive patients; p=0.031 for EFS, p=0.033 for PFS}. Also, Landau et al. (2020) [27] , who conducted a pilot prospective study on Bortezomib and Dexamethasone pre and post risk-adapted autologous stem cell transplantation (ASCT) in 19 untreated AL amyloidosis patients, measured MRD with 10-color MFC (sensitivity up to 10^{-6}), pre, 12 and 24 months post ASCT, and observed superior PFS in MRD negative patients at 1 year (p=0.008).

In general, OS was not significantly different among MRD negative and positive patients. However, Bomsztyk et al. [29] reported that at 12 months, median OS was not reached in FLC-MS negative patients whereas, median OS was 108 months in FLC-MS positive patients (p=0.024).

Summary of Statistically Significant Results

- **Bomsztyk et al., 2020:**Cardiac response: MRD negative 19.6% vs MRD positive 9% (p = 0.0162)
- Renal response: MRD negative 38% vs MRD positive not reported (p = 0.015)
- Survival: OS not reached (MRD negative) vs 108 months (MRD positive) (p = 0.024)

Dispenzieri et al., 2020 [26]

- **Disease progression**: MRD negative 13% vs MRD positive 75% at 50 months **(p = 0.003)**

Kastritis et al., 2021 [7]:

- Disease progression (hematologic): MRD negative 0% vs MRD positive 21% (p = 0.029)
- Survival (PFS): MRD negative 96% vs MRD positive 68% (p = 0.026)

Landau et al., 2020 [27]:

- Survival (PFS): Superior for MRD negative at 1 year (p = 0.008)

Li et al., 2022 [30]:

- Cardiac response: MRD negative 93% vs MRD positive 25% (p = 0.019)
- Survival (PFS): MRD negative 76.4 months vs MRD positive 24.5 months (p = 0.004)

Muchtar et al., 2020 [28]:

- Renal response: MRD negative 100% vs MRD positive 68% (p = 0.005)
- Survival (PFS): MRD negative 88% vs MRD positive 28% at 3 years (p < 0.001)

Palladini et al., 2021 [34]:

- Cardiac response: MRD negative 95% vs MRD positive 75% (p = 0.023)

- Renal response: MRD negative 90% vs MRD positive 62% (p = 0.006)
- Disease progression: MRD negative 2% vs MRD positive 26% (p = 0.001)

Sidana et al., 2020 [33]:

- Cardiac response at MRD assessment: MRD negative 67% vs MRD positive 22% (p = 0.04)
- Survival (PFS at 1 year): MRD negative 100% vs MRD positive 64% (p = 0.006)

Xu et al., 2024 [31]:

- Cardiac response: MRD negative 66.7% vs MRD positive 38.1% (p = 0.032)
- Survival: EFS: Not reached (MRD negative) vs 19.9 months (MRD positive) (**p = 0.031**)
- PFS: Not reached (MRD negative) vs 31.3 months (MRD positive) (**p = 0.033**)

Discussion

In this systematic review of 1053 patients in 13 studies, MRD negativity has been consistently associated with improved survival, mainly PFS, in 7 studies [7,26,27,28,29,30,31], favorable cardiac response in 5 studies [29,30,31,33,34], favorable renal response in 3 studies [28,29,34] and reduced disease progression in 3 studies [26,32,34]. These results suggest that MRD negativity in AL amylodosis is a promising prognostic biomarker.

Significance of MRD monitoring is well established in multiple myeloma (MM). Achieving MRD negativity has been consistently associated with longer PFS and OS across MM trials. Munshi et al. [14] reported in a large meta-analysis how MRD negativity was associated with significantly improved survival outcomes regardless of disease setting (newly diagnosed or relapsed/refractory MM), MRD sensitivity thresholds, cytogenetic risk, method of MRD assessment, depth of clinical response at the time of MRD measurement, supporting its candidacy to become a valid prognostic and predictive marker. A recent meta-analysis by Ntanasis-Stathopoulos et al. (2025) also reported negative and strong association between MRD negativity odds ratios and survival hazard ratios (β_PFS = -0.20, $p < 0.001$, β_OS = -0.12, $p = 0.023$), and showed that sustained MRD negativity at 1 year was strongly correlated with prolonged PFS (β_PFS = -0.30, $p < 0.001$). Deep hematologic response with MRD negativity has been validated as a surrogate marker for survival in MM, but for AL amyloidosis, we currently lack large, prospective, uniform studies. Majority of MRD studies in AL amyloidosis are retrospective, single-centered studies with small sample sizes that incorporate variable methods of MRD assessment (flow cytometry vs next-generation sequencing) with different sensitivity thresholds. One of the reasons why large studies have not been so far conducted for AL amyloidosis patients is because it a rare disease. AL amyloidosis is approximately 4–15 times rarer than MM with worldwide incidence of 5.1 to 12.8 cases per million person-years [3].

Also, disease dynamics differ between MM and AL amyloidosis. AL amyloidosis is a low burden plasma clonal disease. Toxic amyloidogenic light chains that eventually cause severe organ damage in heart and the kidneys are actually produced by very low levels of malignant clonal plasma cells. Also, unlike MM, the impact of hematologic progression on survival overshadowed by organ progression. Amyloid induced restrictive cardiomypathy and/or progressive chronic kidney disease with nephrotic range proteinuria impose marked impacts on survival, cardiac failure being the most predominant player in predicting OS. Most patients with hematologic CR continue to have organ dysfunction as organ response lags up 12-24 months after achieving CR. Underlying reasons for organ response delay suggested to be due to persistent irreversible inflammatory process in organs caused by already deposited amyloid fibrils, preservence of amyloid fibrils and low clonal burden nature of this disease. Therefore, deep hematologic response with CR and MRD negativity may not be enough to be a surrogate marker for overall survival in AL amyloidosis. However, incorporation of MRD negativity with organ response markers during prognostic evaluations can provide a composite tool for predicting survival.

Other caveats with MRD assessment in AL amyloidosis arise from methodological challenges. MRD is a broad term for "minimal residual disease". Residual disease can be detected by either revealing low amounts of clonal plasma cells in the bone marrow aspirate vs by detecting low amounts of monoclonal FLCs in the serum that are missed with standard immunofixation electrophoresis (IFE) and immunoassays. There is emerging evidence that mass spectrometry (MS) is more sensitive than conventional IFE and immunoassays for detecting low levels of serum FLCs [36]. Bomsztyk et al. [29] studied the utility of FLC-MS in a large series of 487 patients with AL amyloidosis and reported that out of those achieving a conventional hematologic CR in 6 and 12 months, only 45 (27.7%) and 64 (39%) were FLC-MS negative. Although MS is more sensitive for detecting low levels of serum FLCs, its wide utilization across centers is limited. It is currently only available at specialized laboratories. Mass spectrometry (MS) platforms are complex systems consisting of an ion source, mass analyzer, detector, software, and often combined with a separation technique like liquid chromatography (LC-MS) or gas chromatography (GC-MS) to identify and quantify molecules based on their mass-to-charge ratio. Heterogenicity of these platforms hinder standardization of MS yielding to non-comparable results across studies. Also, due to its high sensitivity, MS can detect small, clinically irrelevant clones leading to potential overdiagnosis or confusion on isotyping of FLC. The use of FLC-MS to assess MRD is attractive given it can be performed on serum samples reducing the need of an invasive procedure, bone marrow biopsy, for MRD assessments.

Multiparameter flow cytometry (MFC) and next generation flow cytometry (NGF) are the most commonly used methods to detect MRD in bone marrow aspirates. The main difference between MFC and NGF is the sensitivity threshold. MFC is widely available and its sensitivity can reach to 10^{-4} to 10^{-5}, depending on the number of colors and events analyzed. Operator expertise and gating strategy can influence reproducibility. NGF is more standartized than MFC as the EuroFlow consortium (EuroFlow) has established standardized antibody panels and analysis protocols. Adhering to EuroFlow guidelines reduces inter-laboratory variability and operator dependibility [37]. NGF's sensitivity is higher at 10^{-5} to 10^{-6}. For both

MFC and NGF, sample collection from the bone marrow aspirate can be challenging due to bone marrow hemodilution, patchy infiltration, delayed processing, and low cellularity all of which are common issues with AL amyloidosis.

Next generation sequencing (NGS) is another emerging method for detecting MRD. Its advantage lies in clonality tracking. NGS can identify the unique rearrangement in the DNA of the malignant plasma cell creating a 'molecular fingerprint' for tracking residual disease. Its sensitivity is high at ~10^{-6}. However, NGS requires initial identification of the clone type, which can be difficult if the bone marrow plasma cell burden is very low, which is usually the case with AL amyloidosis (Cuenca et al., 2021). NGS is also costly and has longer turnaround time than MFC/NGF owing to its complex analysis data sets.

Another problem with interpreting the results of the studies on MRD assessment in AL amyloidosis caused by the non-uniform timing of MRD assessments. In this review, most studies started evaluating MRD status after completion of frontline treatments, while others waited until CR/VGPR achievement and some screened MRD at regular intervals during the treatments (Table 3). The differences at the timing of the MRD assessments make it difficult to compare MRD correlations with clinical outcomes across the studies. Without robust published evidence on MRD utility in AL amyloidosis patients, currently, in clinical practice, there are no guidelines for escalating or de-escalating treatments depending on the MRD status of the patients.

Conclusions and Future Directions

This systematic review highlights the potential value of MRD negativity as a prognostic biomarker in systemic AL amyloidosis patients who have achieved CR or VGPR. Overall, MRD negativity consistently predicted higher organ response, lower disease progression and improved progression free survival in the 13 studies reviewed. However, evidence is limited due to small samples sizes, retrospective nature of most studies, use of variable MRD assays without standardized protocols, and non-uniform timing of MRD testing. In summary, although MRD negativity is a validated surrogate for survival in MM, its candidacy as a prognostic biomarker or a survival surrogate in AL amyloidosis bears potential challenges despite tendency of favorable outcomes observed with MRD negative patients in limited published studies. Since AL amyloidosis is a rare disease, studies with AL amyloidosis patients are often small sized, single-centered studies. Also, most of the MRD data in AL amyloidosis comes from retrospective studies. Comparison of results across the studies is difficult due to heterogenicity of MRD detection methods (MFC, NGF, NGS, MS) used in the studies. There is no consensus on when to screen for MRD or how to incorporate MRD status in the treatment strategies. Conversion of MRD negativity to positivity can potentially alarm clinicians to escalate treatments, whereas sustained MRD negativity may promote treatment de-escalation. Future directions for establishing MRD utility in AL amyloidosis patients would include planning and conducting large scale, multi-centered, prospective clinical trials that use standardized and reproducible methods for MRD detection, with predefined MRD assessment time points to be able to homogeneously evaluate correlations of MRD status with clinical outcomes.

Also, in the era of artificial intelligence (AI), machine learning (ML) and deep learning (DL) tools can be incorporated to increase the sensitivity of MRD detecting methods in AL amyloidosis. For example, AI assisted flow cytometry (MFC/NGF) gating and clustering algorithms can recognize rare clonal plasma cell immunophenotypes that might be missed with manual analysis [16]. Also, AI based automated flow cytometry analysis reduces operator variability and turnover time. AI assisted mass spectrometry can enhance identification of faint monoclonal FLCs with low peaks as ML models get trained to filter high intensity background noise of polyclonal immunoglobulins. Again, automation of data analysis with AI diminishes operator variability.

AI and ML algorithms can analyze extensive, complex NGS datasets faster than traditional methods. NGS data can contain background noise due to sequencing artifacts and AI can use advanced error modeling to differentiate true clonal sequences from artifacts, improving detection sensitivity which is essential for low clonal burden diseases such as AL amyloidosis.

MRD negativity falls short to be a survival surrogate in AL amyloidosis despite its validation in MM since organ involvement, especially cardiac involvement, plays a major role in predicting prognosis and survival. To overcome this drawback, AI tools can integrate multimodal data including blood and urine biomarkers such as serum N-terminal pro-B-type natriuretic peptide (NT-proBNP), high sensitivity cardiac troponin (hs-cTn), urine protein, and imaging data such as from cardiac magnetic resonance imaging (MRI), echocardiogram, positron emission tomography-computed tomography (PET-CT) to form a composite biomarker which can predict survival more accurately. Conducting large scale, multi-centered, prospective clinical trials, standardization of MRD detection methods, integration of AI to increase sensitivity of MRD detection methods and creating a composite biomarker will all increase the likelihood of validation of MRD and incorporation of it in clinical decision in AL amyloidosis.

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