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Diagnostic Value of Bone Marrow Smear for Amyloid Detection and Its Correlation with Clinical Features in Systemic Light-Chain Amyloidosis

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KEYWORDS

Systemic light-chain amyloidosis; Bone marrow smear; Bone marrow biopsy; Wright–Giemsa; Congo red

Abstract

This study aimed to evaluate the diagnostic value of bone marrow smear in systemic light chain (AL) amyloidosis and to investigate the correlation between bone marrow amyloid deposition and clinical characteristics. A total of 252 patients with AL amyloidosis were enrolled, including 126 with positive bone marrow biopsies and 126 with negative biopsies. Bone marrow smear detected amyloid deposits in 121 of 252 patients (48.0%). Among the 126 patients with positive bone marrow biopsies, 121 (96.0%) had positive smears; among the 126 patients with negative biopsies, all 126 (100%) had negative smears. The overall concordance between smear and biopsy was 98.0% (247/252). In the AL group without concomitant plasma cell or B-cell disorders, bone marrow amyloid deposition was significantly associated with λ light chain type, lower hemoglobin levels, and elevated levels of ALP, GGT, β2-MG, and NT-proBNP, suggesting a correlation with impaired liver, kidney, and cardiac function. Survival analysis indicated that bone marrow amyloid deposition had no significant impact on prognosis. Bone marrow smear may serve as a rapid screening tool for AL amyloidosis, and its combination with biopsy could enhance diagnostic efficiency.

Introduction

Amyloidosis is a rare, heterogeneous disorder characterized by the deposition of misfolded proteins in tissues and organs, leading to disruption of tissue architecture and organ dysfunction. Amyloid deposits consist of soluble globular proteins that misfold and aggregate into insoluble fibrillar aggregates, causing progressive tissue and organ damage, and ultimately patient death [1]. Amyloid protein typically deposits within the extracellular matrix and is defined by the following features: exhibiting brick-red coloration under normal light microscopy after Congo red staining; displaying apple-green birefringence under polarized light microscopy; appearing as non-branching, randomly arranged fibrils 8–14 nm in diameter under electron microscopy; and revealing a β-pleated sheet conformation by X-ray diffraction microscopy [2].

Amyloid deposition can affect multiple organs and tissues, including the kidneys, heart, liver, skin and soft tissues, gastrointestinal tract, peripheral nerves, lungs, and glands. To date, 36 distinct types of amyloid proteins have been identified [3]. In China, systemic light chain amyloidosis is the most common type of systemic amyloidosis in clinical practice. Its fibrils derive from immunoglobulin light chains or their fragments [4]. Bone marrow involvement by amyloid protein is also frequently observed [5].Definitive diagnosis of amyloidosis requires histopathological examination of biopsy specimens. Biopsies are typically obtained from symptomatic organs/tissues or readily accessible sites such as abdominal fat, bone marrow, or salivary glands. However, biopsy sampling from symptomatic organs often carries significant risks, particularly cardiac biopsy, which patients are often reluctant to undergo.

Bone marrow biopsy is a standard diagnostic procedure for most hematological disorders and a well-tolerated approach for diagnosing amyloidosis [6-7]. However, its specimen processing is cumbersome, the reporting time is prolonged, and its positivity rate is lower in domestic settings compared to international reports. If amyloid protein can be detected in bone marrow biopsy specimens, a pertinent question arises: could corresponding changes be observed in bone marrow smears? Case reports have indeed documented the detection of amyloid protein in bone marrow smears [8]. This prompts further investigation into the sensitivity of amyloid detection on smears compared to biopsy and the clinical implications of amyloid presence in smears. To date, no large-scale studies have addressed these questions.This study reanalyzed bone marrow smears from 252 patients with systemic AL amyloidosis. It aims to assess the diagnostic utility of amyloid protein detection in smears and to explore potential correlations between bone marrow amyloid

deposition, organ involvement, and clinical characteristics.

Patients, materials, and methods

We retrospectively studied bone marrow smears from 252 patients diagnosed with systemic light chain (AL) amyloidosis at the First Affiliated Hospital, Zhejiang University School of Medicine. Among these patients, 180 had no accompanying plasma cell or B-cell disorders, while 72 had accompanying disorders (including 1 with lymphoplasmacytic lymphoma and 71 with multiple myeloma).

In the 180 patients without accompanying plasma cell/B-cell disorders, 78 were treatment-naïve with positive bone marrow amyloid, 75 were treatment-naïve with negative bone marrow amyloid, and 27 were follow-up patients after treatment with negative bone marrow amyloid. Among the 72 patients with accompanying disorders, 21 were treatment-naïve with positive bone marrow amyloid, 28 were follow-up patients after treatment with positive bone marrow amyloid, 19 were treatment-naïve with negative bone marrow amyloid, and 4 were follow-up patients after treatment with negative bone marrow amyloid.

Of these 252 patients, 126 had positive bone marrow biopsies and 126 had negative bone marrow biopsies. The diagnostic performance of bone marrow smear was evaluated by comparing its results with those of concurrent bone marrow biopsy. Since all patients had a confirmed diagnosis of systemic AL amyloidosis, biopsy-negative cases represent false negatives of biopsy rather than true absence of disease. Therefore, we report the detection rate of bone marrow smear (proportion of all patients with positive smears) as well as the concordance between smear and biopsy results.Bone marrow biopsy tissue and bone marrow smear specimens were obtained simultaneously from the same anatomical site for each patient. For each patient, two bone marrow smears were subjected to Wright-Giemsa staining and two to Congo red staining.The two Wright-Giemsa stained smears were examined under a normal light microscopy for plasma cell counting and detection of amyloid deposits. The two Congo red stained smears were assessed for positivity or negativity using polarized light microscopy. Utilizing two smears per stain aimed to minimize procedural variability and enhance result reliability.Congo red staining was performed on either freshly prepared or archived smears. Under standard preservation conditions, archived smears stored in well-ventilated and dry conditions within paper envelopes housed in metal cabinet drawers did not compromise staining quality.Additionally, we included bone marrow smears from 50 patients with non-amyloidosis-related conditions as negative controls. This control group comprised 10 bone marrow donors, 10 patients with acute myeloid leukemia (AML), 10 with chronic myeloid leukemia (CML), 10 with acute lymphoblastic leukemia (ALL), and 10 with immune thrombocytopenia (ITP).

In this study, Wright–Giemsa-stained bone marrow smears were first

screened at 100× magnification under a normal light microscope to identify amyloid deposits, characterized by clumpy, sheet-like, dot-like, linear, or irregularly distributed material. Suspected areas were further examined at 1000× magnification to confirm the presence of amorphous purplish-blue material. The same procedure was applied to Congo red-stained smears to detect brick-red amorphous deposits. Finally, Congo red-stained smears were assessed under polarized light microscopy; apple-green birefringence was considered positive for amyloid, while its absence indicated a negative result. All evaluations were independently performed by three experienced hematologists, each with over ten years of expertise in bone marrow morphology. A consensus among all three was required to assign a positive or negative diagnosis.

Multiparametric flow cytometry (MFC) was employed for the detection of clonal plasma cells in bone marrow. Additionally, cytogenetic karyotyping, fluorescence in situ hybridization (FISH) abnormalities, and survival analysis of the patients were performed. Blood and urine parameters were also analyzed, including white blood cell count (WBC), neutrophil (N), lymphocyte (L), monocyte (M), hemoglobin (Hb), platelet count (PLT), alkaline phosphatase (ALP), gamma-glutamyl transferase (γ-GGT), lactate dehydrogenase (LDH), serum albumin (Alb), serum globulin (Glo), serum free kappa light chains, serum free lambda light chains, serum free kappa/lambda light chain ratio, serum β2-microglobulin (β2-MG), N-terminal pro-brain natriuretic peptide (NT-proBNP), urinary free kappa light chains, urinary free lambda light chains, 24-hour urine total protein, 24-hour urine protein quantification, and urinary β2-microglobulin (β2-MG).

Statistical analysis was performed using SPSS software (version 26). Normally distributed measurement data are expressed as mean ± standard deviation, non-normally distributed measurement data as median, and categorical data as number (percentage). Comparisons of measurement data between groups were conducted using the independent samples t-test, while comparisons of categorical data were performed using Pearson's chi-square test. Survival analysis was carried out using the Kaplan–Meier method. A P-value < 0.05 was considered statistically significant.

All methods were performed in accordance with the relevant guidelines and regulations, including the principles of the Declaration of Helsinki.

Results

1.Among the 126 patients with positive biopsies, bone marrow smear examination revealed suspected amorphous purple-blue material in 121 cases, with similar deposits observed within plasma cells in one case (Figure 1). All 121 smear-positive specimens exhibited characteristic apple-green birefringence under polarized light following Congo red staining (Figure 2). Among the 126 patients with negative biopsies, no

amyloid deposits were detected in any of the bone marrow smears, and none showed characteristic apple-green birefringence under polarized light after Congo red staining.

Among all 252 patients with systemic AL amyloidosis, bone marrow smear detected amyloid deposits in 121 patients (48.0%). Of the 126 patients with positive bone marrow biopsies, 121 (96.0%) had positive smears. Of the 126 patients with negative biopsies, all 126 (100%) had negative smears. The overall concordance between smear and biopsy results was 98.0% (247/252).

2. All treatment-naïve patients were stratified into two groups based on the presence or absence of bone marrow amyloid deposition: those without concomitant plasma cell or B-cell disorders and those with concomitant plasma cell or B-cell disorders. Their baseline clinical characteristics are summarized in Table 1.

3. Comparison of patients with and without bone marrow amyloid deposition

In the group of amyloidosis patients without concomitant plasma cell/B-cell disorders (n=180), patients with bone marrow amyloid deposition, compared to those without, exhibited significantly higher proportions of the λ light chain isotype and IgG isotype, as well as significantly lower hemoglobin levels. Notably, levels of alkaline phosphatase (ALP), γ-glutamyl transferase (GGT), serum β2-microglobulin (β2-MG), and N-terminal pro-brain natriuretic peptide (NT-proBNP) were also significantly elevated in the amyloid-positive subgroup. Detailed comparisons are shown in Table 2 (Characteristics of Peripheral Blood Cells), Table 3 (Serum biochemical parameters), Table 4 (Urinary parameters), and Table 5 (Cytogenetic abnormalities).

In the group of amyloidosis patients with concomitant plasma cell/B-cell disorders (n=72), no significant differences were observed between amyloid-positive and amyloid-negative patients across any of the evaluated parameters (Tables 2-5).

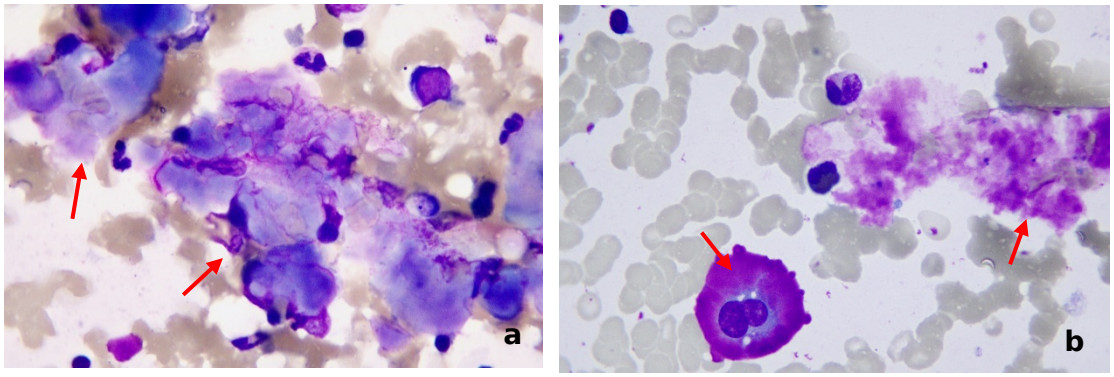

Figure 1. In bone marrow smears, amyloid deposits appear as amorphous, indistinct, purplish blue material upon Wright-Giemsa staining and can also be observed within plasma cells. Original magnification ×100.

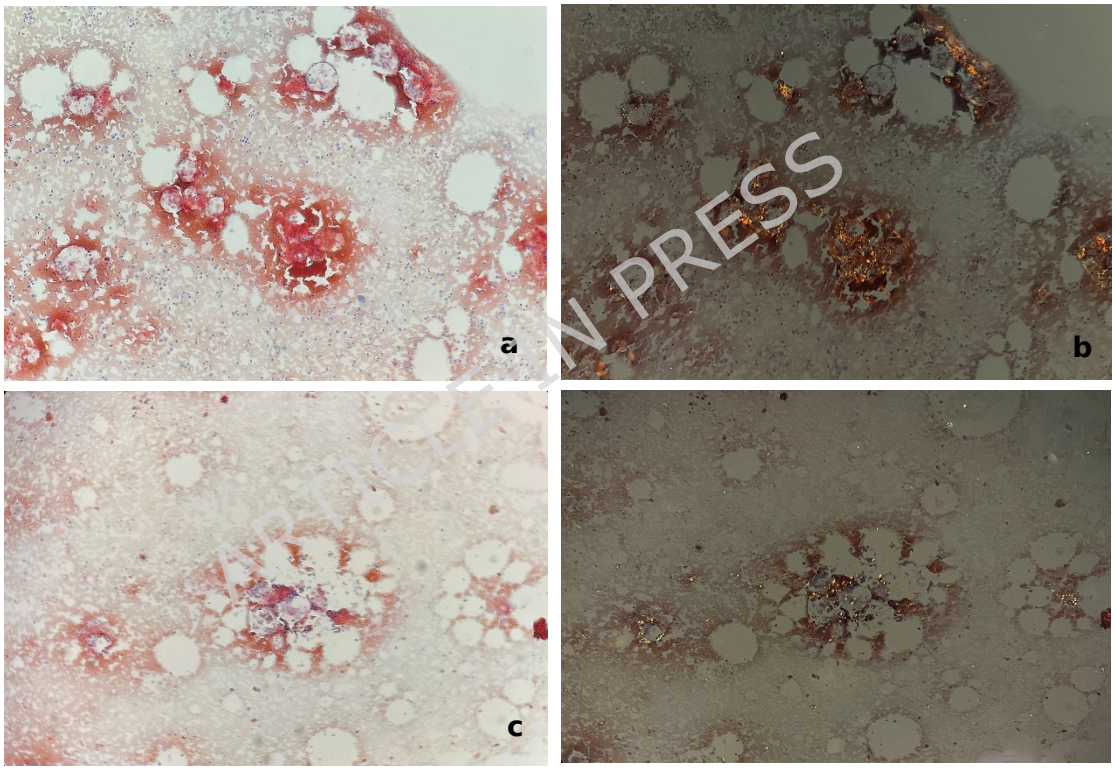

Figure 2. In bone marrow smears, diffuse and focal amyloid deposits exhibit a characteristic brick red coloration under normal light microscopy following Congo red staining (a, c). Corresponding areas exhibiting classic apple-green birefringence under polarized light microscopy. (b, d). Original magnification: ×100.

Table 1 Clinical characteristics of patients with and without amyloid infiltration on bone marrow smears. Data are presented as absolute numbers (percentages).

Item	AL amyloidosis without concomitant plasma cell/B-cell disorders (n=151)		AL amyloidosis with concomitant plasma cell/B-cell disorders (n=42)		P	
	Amyloid(+)	Amyloid(-)	Amyloid(+)	Amyloid(-)	P 1	P 2
Total number of patients	78(52%)	73(48%)	20(48%)	22(52%)		
Median age in years	63.5	64	65	61.5		
(range)	(37-87)	(44-84)	(36-83)	(37-73)	0.818	0.160
Sex						
Male/ Female	46/32	50/25	12/9	6/13	0.325	0.105
Clinical organ involvement						
Median number involved	3	2	2	2	0.166	0.572
Heart	36 (46.15%)	28 (37.33%)	6 (28.57%)	9(47.37%)	0.269	0.220
Kidney	60 (76.92%)	59 (78.67%)	12 (57.14%)	12 (63.16%)	0.795	0.698
Liver	7 (8.97%)	2 (2.74%)	1 (4.76%)	2 (10.53%)	0.189	0.928
Lung	0	1 (1.33%)	0	0	0.49	-
Peripheral neuropathy	3 (3.85%)	2 (2.74%)	0	0	1.00	-
Gastrointestinal	3 (3.85%)	3 (4.11%)	0	1 (5.26%)	0.674	0.475
Soft tissue	6 (7.69%)	1 (35.62%)	3 (14.29%)	3 (15.79%)	0.135	1.00
Subtype						
IgG	19(24.36%)	30(40%)	10(47.62%)	5(26.32%)	0.038	0.165
IgA	11(14.10%)	11(14.67%)	3(14.28%)	6(31.58%)	0.921	0.353
Ig(-)	48(61.54%)	34(45.33%)	7(33.33%)	8(42.11%)	0.045	0.567
λ	52(66.67%)	62(82.67%)	17(80.95%)	15(78.95%)	0.023	1.00
κ	26(33.33%)	13(17.33%)	4(19.05%)	4(21.05%)	0.023	1.00
BM plasma cells (%)						
Morphological Cell Count	4.56±2.99	4.91±4.1	14.10±13.84	10.92±11.5	0.547	0.438
MFC Assay	1.61±1.97	1.41±2.05	4.44±5.60	4.42±5.36	0.533	0.990

P1:comparison between amyloid-positive and amyloid-negative patients within the group without concomitant plasma cell/B-cell disorders. P2: comparison between amyloid-positive and amyloid-negative patients within the group with concomitant plasma cell/B-cell disorders.

Table 2 Characteristics of Peripheral Blood Cells in Patients with Bone Marrow Amyloid Deposition

Item	AL amyloidosis without concomitant plasma cell/B-cell disorders (n=151)		AL amyloidosis with concomitant plasma cell/B-cell disorders (n=42)		P	
	Amyloid(+)	Amyloid(-)	Amyloid(+)	Amyloid(-)	P 1	P 2
White blood cells						
(X 10^9/L)	7.21±2.46	7.11±2.38	6.57±1.80	6.47±2.41	0.792	0.888
N(%)	65.76±12.21	63.29±11.51	65.26±9.62	62.19±13.88	0.206	0.449
M(%)	7.32±3.22	7.40±2.73	8.78±3.36	8.34±4.92	0.873	0.746
L(%)	24.56±10.08	25.82±9.75	21.64±7.45	27.21±11.19	0.442	0.094
Hemoglobin (g/L)	117.90±23.70	125.96±23.73	102.48±21.09	107.94±20.62	0.038	0.420
Platelets(X 10^9/L)	241.04±115.21	227.26±92.31	273.29±123.16	217.06±147.25	0.420	0.202

P1:comparison between amyloid-positive and amyloid-negative patients within the group without concomitant plasma cell/B-cell disorders. P2: comparison between amyloid-positive and amyloid-negative patients within the group with concomitant plasma cell/B-cell disorders.

Table 3 Serum biochemical parameters in patients with bone marrow amyloidosis

Item	AL amyloidosis without concomitant plasma cell/B-cell disorders (n=151)		AL amyloidosis with concomitant plasma cell/B-cell disorders (n=42)		P	
	Amyloid(+)	Amyloid(-)	Amyloid(+)	Amyloid(-)	P 1	P 2
ALP (U/L)	171.43±195.83	91.63±50.6	146.85±178.37	144.29±214.76	0.010	0.969
γ-GGT (U/L)	169.01±284.32	88±181.55	131.3±247.65	87±159.43	0.041	0.53
LDH (U/L)	270.79±89.94	258±147.48	237.11±95.37	343.75±348.73	0.530	0.253
Alb (g/L)	29.03±7.73	30.28±8.64	34.52±11.58	34.32±10.01	0.354	0.953
Glo (g/L)	23.90±6.58	25.09±6.2	30.47±16.88	25.61±13.33	0.257	0.330
κ (mg/dL)	373.68±383.78	336.17±199.52	216.89±150.65	248.52±195.94	0.479	0.595
λ (mg/dL)	261.52±214.07	309.22±210.26	524.42±979.75	438.18±539.18	0.195	0.751
κ/λ	1.82±1.99	1.51±1.35	1.46±2.10	1.16±0.96	0.303	0.588
β2-MG (mg/L)	6.72±5.61	3.66±2.32	7.03±5.69	4.06±3.59	0.003	0.095
NT-proBNP（pg /mL）	3211.87±3411.11	1718.17±2494.60	4523.9±4308.95	1749.27±2497.86	0.020	0.096

P1:comparison between amyloid-positive and amyloid-negative patients within the group without concomitant plasma cell/B-cell disorders. P2: comparison between amyloid-positive and amyloid-negative patients within the group with concomitant plasma cell/B-cell disorders.

Table 4 Urinary parameters in patients with bone marrow amyloidosis

Item	AL amyloidosis without concomitant plasma cell/B-cell disorders (n=151)		AL amyloidosis with concomitant plasma cell/B-cell disorders (n=42)		P	
	Amyloid(+)	Amyloid(-)	Amyloid(+)	Amyloid(-)	P 1	P 2
protein(g/L)	3.03±4.42	2.75±2.49	2.78±4.58	1.49±1.56	0.682	0.457
protein (g/d)	2.75±2.67	3.70±4.23	5.77±10.28	1.52±1.63	0.304	0.386
κ(mg/dL)	16.45±20.25	12.59±15.54	28.54±60.89	5.66±8.35	0.221	0.144
λ(mg/dL)	33.82±77.45	20.07±39.33	24.86±44.74	59.88±89.65	0.194	0.174
β2-MG (g/mol Cr)	0.534±1.24	1.33±3.21	3.75±6.3	0.56±1.17	0.180	0.201

P1:comparison between amyloid-positive and amyloid-negative patients within the group without concomitant plasma cell/B-cell disorders. P2: comparison between amyloid-positive and amyloid-negative patients within the group with concomitant plasma cell/B-cell disorders.

Table 5 Cytogenetic abnormalities detected by G-banding and FISH in patients with bone marrow amyloid deposition

Item	AL amyloidosis without concomitant plasma cell/B-cell disorders (n=151)		AL amyloidosis with concomitant plasma cell/B-cell disorders (n=42)		P	
	Amyloid(+)	Amyloid(-)	Amyloid(+)	Amyloid(-)	P 1	P 2
G band abnormality	4 (9.52%)	1 (2.56%)	1 (33.33%)	1 (12.5%)	0.402	0.491
FISH abnormality	3(25%)	13(54.17%)	8(88.89%)	6(66.67%)	0.157	0.576
IgH(14q32) translocation	3(25%)	10(41.67%)	2(22.22%)	1(11.11%)	0.468	1.000
Amplification of 1q21	2(16.67%)	8(33.33%)	8(33.33%)	4(44.44%)	0.438	0.637
Deletion of P53(17p13.1)	0	3(12.5%)	1(11.11%)	2(16.67%)	0.536	1.000
Deletion of RB1(13q14)	0	2(16.67%)	2(16.67%)	3(16.67%)	0.543	1.000
Deletion of D13S319	0	3(12.5%)	3(33.33%)	4(33.33%)	0.536	1.000
IGH/CCND1,t(11;14)	0	3(12.5%)	0	0	0.536	-

P1:comparison between amyloid-positive and amyloid-negative patients within the group without concomitant plasma cell/B-cell disorders. P2: comparison between

amyloid-positive and amyloid-negative patients within the group with concomitant plasma cell/B-cell disorders.

Survival Analysis

The group of AL amyloidosis patients without concomitant plasma cell/B-cell disorders

After a mean follow-up of 40 months, no significant difference in survival was demonstrated between patients with amyloid deposits in the bone marrow (n=57) and those without amyloid deposits (n=57). Please see Figure 3.

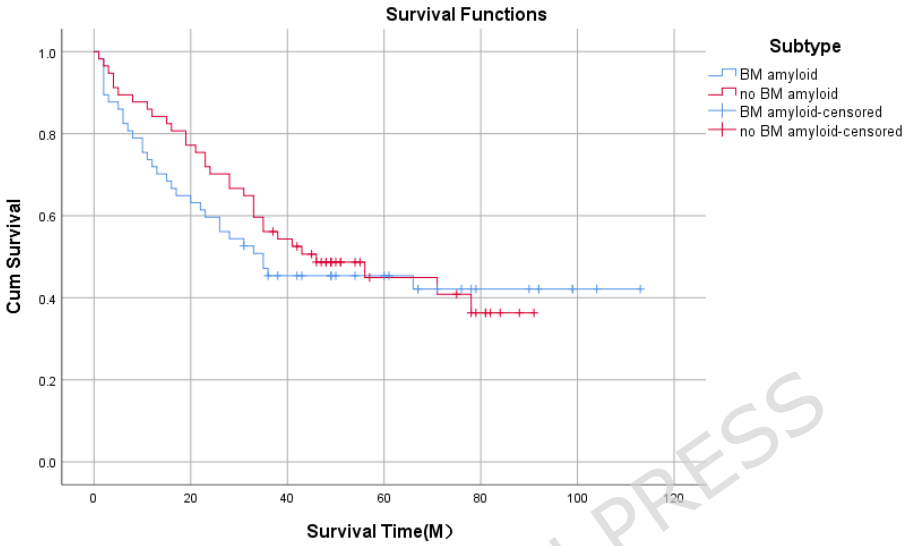

Figure 3. Kaplan–Meier survival analysis comparing all treatment-naïve patients with and without amyloid on BM (p=0.599).

The group of AL amyloidosis patients with concomitant plasma cell/B-cell disorders

After a mean follow-up of 38 months, no significant difference in survival was demonstrated between patients with amyloid deposits in the bone marrow (n=17) and those without (n=14). Please see Figure 4.

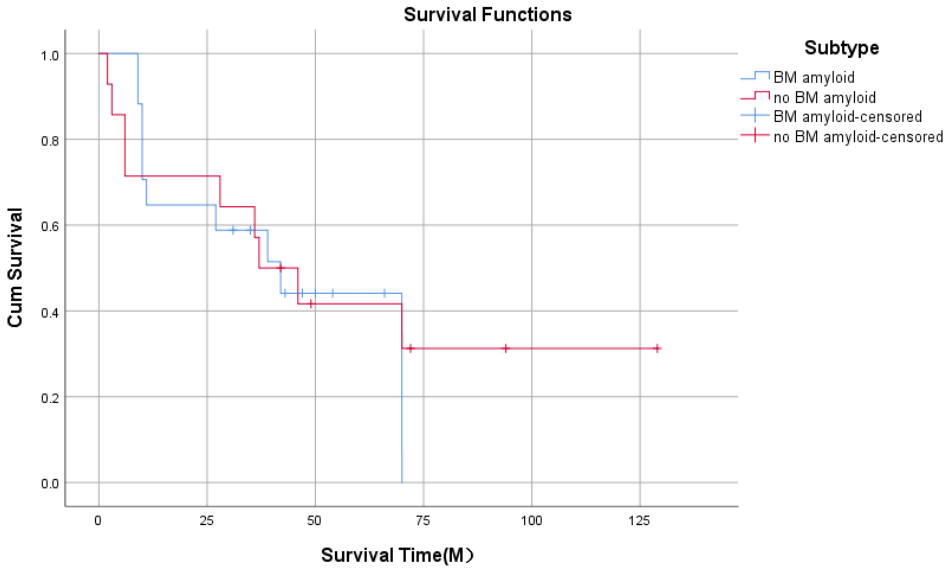

Figure 4. Kaplan–Meier survival analysis comparing all treatment-naïve patients with and without amyloid on BM (p=0.913).

Discussion

Systemic AL amyloidosis is a relatively rare and highly heterogeneous disease with an unclear pathogenesis. It is characterized by the deposition of amyloid protein in the extracellular matrix, leading to tissue and organ damage at deposition sites. The disease progresses rapidly and is associated with high mortality. Its incidence in China has been increasing annually [4]. Moreover, systemic AL amyloidosis has a high rate of erroneous diagnosis; one study indicated that approximately 72% of patients experience a diagnostic delay of at least one year from symptom onset [8]. Approximately 25% of patients already have severe, irreversible cardiac damage at the time of diagnosis and die within the first year after diagnosis [9]. Therefore, early diagnosis and prompt initiation of treatment are crucial for improving outcomes and survival in this patient population.

The majority of patients with systemic AL amyloidosis exhibit bone marrow involvement [10], which is typically confirmed by bone marrow biopsy. However, few previous studies have utilized bone marrow smear cytology for diagnosis.

Our observations showed that among the 126 biopsy-positive patients, amorphous purple-blue material was detected on bone marrow smears in 121 cases, all of which were positive for Congo red staining. In all 126 biopsy-negative patients, no amyloid deposits were detected on bone marrow smears, and Congo red staining was negative in all cases. Additionally, all smears used as negative controls were devoid of these changes. Thus, the findings of this study indicate that patients with suspected amyloid deposits on Wright-Giemsa stained bone marrow smears were consistently positive for Congo red staining on bone marrow biopsy, while those without suspected deposits on smears were negative on biopsy. In our cohort, bone marrow smear detected amyloid deposits in 48.0% of all patients. Among patients with positive bone marrow biopsies, the detection rate of smear was 96.0%, and among those with negative biopsies, all had negative smears, yielding an overall concordance of 98.0% between the two methods. These findings indicate that while bone marrow smear is less sensitive than biopsy for detecting amyloid deposits (48.0% vs. 50.0% biopsy positivity rate), the two methods show excellent agreement when biopsy is positive. Furthermore, compared with bone marrow biopsy, bone marrow smear cytology is less invasive and requires shorter processing time. Its additional advantage lies in the fact that even in the absence of clonal analysis, this limitation can be overcome through flow cytometric analysis [11-12]. Petruzziello, F. [13] et al. suggested that cytological evaluation may be more sensitive than histological analysis because aspirates used for smears may originate from a broader area, whereas histological sections cover only a limited region. Thus, the likelihood of encountering small and sporadic amyloid deposits is higher

in cytological samples. Siragusa et al. [14] also reported a lower positivity rate in histological findings. However, some researchers hold opposing views. Christoph K et al. [15] argue that bone marrow smear cytology should not be used as the primary screening tool for systemic AL amyloidosis, as the sensitivity of Congo red staining is far lower than that of routine bone marrow pathological examination. We believe that these discrepancies in reported sensitivity may be attributable to the following key factors:

First, staining methodology and interpretation criteria play a critical role. As emphasized by Bowen et al., the choice of Congo red staining technique (e.g., Highman's method vs. alkaline method), tissue fixation protocols, and the experience of the interpreting pathologist can significantly influence detection rates. Second, institutional experience and dedicated slide review—such as prolonged observation time and consensus evaluation by multiple pathologists—have been shown to improve diagnostic sensitivity[16].

Given the 98.0% overall concordance between bone marrow smear and biopsy findings in our cohort, we propose that Congo red staining of bone marrow smears could serve as an ancillary diagnostic tool. This may be especially relevant in centers where optimized staining techniques and experienced interpretation are available. While we agree that it should not replace fat aspiration or bone marrow histology as first-line methods, our data indicate that it can provide meaningful diagnostic information in a substantial proportion of patients.

All treatment-naïve patients were stratified into two groups based on the presence or absence of bone marrow amyloid deposition: those without concomitant plasma cell or B-cell disorders and those with concomitant plasma cell or B-cell disorders. No significant differences were observed between the two groups in terms of patient age or organs involved, a finding that is inconsistent with the results reported by Christoph K. et al. [15] and Cowan et al. [17]. This discrepancy may be attributed to the fact that previous studies did not stratify patients by the presence of concomitant hematologic disorders.

In the group of AL amyloidosis patients without concomitant plasma cell/B-cell disorders, patients with bone marrow amyloid deposition had a significantly lower proportion of IgG-type amyloidosis and a significantly higher proportion of κ light-chain type. Furthermore, these patients exhibited significantly elevated levels of serum alkaline phosphatase (ALP), γ-glutamyl transferase (GGT), β2-microglobulin, and N-terminal pro-brain natriuretic peptide (NT-proBNP), suggesting a potential association between bone marrow amyloid deposition and involvement of the liver, kidneys, and heart. Although the extent of organ involvement did not differ significantly, patients with bone marrow amyloid deposits showed trends toward worse hepatic, renal, and cardiac function parameters. Additionally,

hemoglobin levels were significantly lower in this subgroup, indicating that amyloid deposition may adversely affect bone marrow hematopoiesis. These parameters may serve as useful indicators for assessing disease severity.

In the group of AL amyloidosis patients with concomitant plasma cell/B-cell disorders, aside from one case of lymphoplasmacytic lymphoma, the remaining 39 patients had multiple myeloma (MM). No significant differences were observed across any tested parameters, a finding likely attributable to the predominance of MM in this cohort. Petruzziello et al. [13] reported similar results when evaluating the impact of bone marrow amyloid deposition in MM patients, noting no statistically significant associations with commonly used diagnostic or staging parameters. This suggests that bone marrow amyloid deposition may have limited clinical significance in patients with concomitant plasma cell disorders.

Based on our data, the presence of bone marrow amyloid deposition in systemic AL amyloidosis patients did not demonstrate a significant impact on prognosis. Furthermore, no associations were found with abnormal chromosomal karyotypes or fluorescence in situ hybridization (FISH) abnormalities. No significant difference in survival was observed between the two groups (AL amyloidosis patients without concomitant plasma cell/B-cell disorders group: median follow-up 40 months, range 1–113 months; AL amyloidosis patients with concomitant plasma cell/B-cell disorders group: median follow-up 38 months, range 2–129 months). These findings are consistent with those of Petruzziello et al. [18] and Christoph K. et al. [15]. Based on this study, bone marrow smear detection of amyloid deposits can serve as a rapid screening tool for systemic AL amyloidosis, with an overall detection rate of 48.0%. While this is lower than the 50.0% detection rate of bone marrow biopsy, the high concordance (96.0%) between the two methods in biopsy-positive cases suggests that when amyloid is detected on smear, it reliably indicates true disease. Therefore, smear examination may be particularly useful as an adjunctive tool, especially in settings where immediate biopsy is not feasible or while awaiting biopsy results. We recommend that institutions incorporate routine amyloid screening into bone marrow cytology examinations; when suspicious amyloid material is observed on Wright–Giemsa-stained smears, Congo red staining should be performed immediately to confirm the diagnosis.However, it must be emphasized that bone marrow biopsy remains the primary method for the definitive diagnosis of systemic AL amyloidosis. Only through bone marrow biopsy tissue can immunohistochemistry or mass spectrometry be performed to determine the light chain restriction of the amyloid deposits—thereby completing subtyping, which is an absolute prerequisite for accurate diagnosis, risk stratification, and selection of targeted therapy.Thus, bone marrow smear and bone marrow biopsy should be regarded as complementary approaches:

smears are used for initial screening, while biopsy is essential for confirmation and subtyping. The combination of both methods is expected to provide a more timely, accurate, and cost-effective diagnostic pathway for patients with amyloidosis in China.

Author contributions

Conceptualization, Yang M.; methodology, Chang Z.; software, Wang H.; validation,Tang Q. andTang M.; formal analysis, Gao X.; investigation, Yuan S.; resources, Shen D.; data curation, Zhang T.; writing—original draft preparation, Li J.; writing—review and editing, Tong H. and Jin J.; visualization, Tong J.,Xu Y. and Zhao S.; supervision, Zhu Y.; projectadministration, Chang Z. All authors have read and agreed to the published version of the manuscript.

Ethics declarations

Ethics approval

This study was approved by the Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (Approval No.[2025] IIT Ethics Approval No.1377). As the research involved only archived samples and retrospective data collection, the requirement for informed consent was waived by the ethics committee.

Competing interests

The authors declare no competing interests.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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