Original Research Article

CLINICAL AND LABORATORY PROFILE OF AL AMYLOIDOSIS AND TREATMENT OUTCOMES: EXPERIENCE FROM A TERTIARY CARE INSTITUTE IN NORTH INDIA

ABSTRACT

Aims: Primary (AL) amyloidosis is a form of systemic amyloidosis, causing organ dysfunction, mainly affecting the heart and kidney. Early recognition and diagnosis is critical in AL amyloidosis management. This study aimed to describe the clinical and laboratory profile and treatment pattern and outcomes in adult patients (>18 years) diagnosed with AL amyloidosis.

Study design: Retrospective observational study

Place and duration of study: Department of Hematology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India, between 2007-2018.

Methodology: Retrospectively,11 year follow-up data (2007-2018) was retrieved from the electronic medical records.

Results: The study population had a median age of 52 years and 60.6% were males. Heart and kidneys were the most frequently effected organs.Cardiac involvement is the most important determinant of clinical outcome in patients with primary amyloidosis in general and was also associated with poor outcome in this cohort of patients.Of the 33 eligible patients included in the study 9 patients underwent treatment. Bortezomib-based regimen (CyBorD) was the preferred first-line treatment (27.3% patients).Overall,6.0% of the patients presented a deep response (complete or very good partial response). There is limited real-world evidence data from India regarding the prevalence and treatment outcomes for AL amyloidosis due to underdiagnosis and late presentation.

Conclusion: This study provides vital real-world evidence of prevalence and treatment outcomes in primary amyloidosis patients in India.

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Keywords : Primary AL amyloidosis, renal amyloidosis, cardiac amyloidosis, treatment outcomes, India

1.INTRODUCTION

Primary (AL) amyloidosis is the most common form of systemic amyloidosis [1,2]. In AL amyloidosis, amyloid fibrils are formed due to the misfolding of the amyloidogenic light chains, which are produced by the clonal population of plasma cells in the bone marrow [3]. The amyloid fibrils accumulate in various tissues and organs, eventually causing malfunction and organ failure. AL amyloidosis is a rare condition, with an estimated prevalence of 51.27 per million individuals worldwide [2]. The prognosis of AL amyloidosis is poor, with a median survival of approximately 13 months in untreated patients [6]. The heart and kidney are the most commonly affected organs (70%cases) in AL amyloidosis, followed by liver and soft tissue (17%), autonomic nervous system (15%) and gastrointestinal tract (10%) [7].

Treatment of AL amyloidosis aims to promptly reduce the supply of newly formed amyloidogenic monoclonal light chains by suppressing the aberrant amyloidogenic clone, consequently reducing the formation of fibrils which allows gradual organ function recovery and improved survival [8]. Currently, there are limited drugs exclusively approved by the health authorities for AL amyloidosis [9,10]. The practice guidelines, however, offer a wide range of therapeutic modalities [11]. The therapeutic landscape for AL amyloidosis has evolved over the years, since the introduction of melphalan, autologous stem cell transplant (ASCT) and conventional chemotherapies. In this scenario, novel strategies like bortezomib (a proteasome inhibitor), lenalidomide-based regimens, and most recently, daratumumab–a human IgG1κ monoclonal antibody that targets the CD38 surface antigen on the plasma cells–have become important therapeutic options. Also, the Food and Drug Administration (FDA)—the US health regulatory agency—recently approved the first treatment combination specifically indicated for AL amyloidosis treatment (daratumumab plus cyclophosphamide, bortezomib and dexamethasone[12].

Since patients with AL amyloidosis are typically prone to treatment-related toxicities, an individualized treatment approach is essential while managing these patients. Initial treatment with high dose melphalan and ASCT showed improvement in the quality of life (QoL) and survival outcomes in patients with AL amyloidosis [13]. However, this treatment is not recommended for all patients due to the cardiac involvement, to the ASCT ineligibility and/or to the non-tolerability to high doses of melphalan. Cardiac involvement and the extent of cardiac involvement are the major determinants of poor outcomes, but other factors such as age, systolic blood pressure, creatinine levels, Eastern Cooperative Oncology Group (ECOG) performance status [14], presence of large pleural effusions and dependency on oxygen [15,16] have also been identified as prognostic factors related to poor outcomes. In such patients, conventional chemotherapy or bortezomib-based therapy is the preferred option [17]. Treatment with bortezomib, melphalan and dexamethasone demonstrates higher rates of complete response (CR) than melphalan and dexamethasone (42% versus 19%) in the AL amyloidosis patients [18]. Bortezomib-alkylator-steroid combination is preferred for patients with advanced disease—cardiac involvement, renal impairment, severe hypoalbuminemia, fluid retention -as they need a more rapid response [11]. Bortezomib

is very effective but still has a significant toxicity profile for advanced cardiac stage patients.
Daratumumab demonstrates a significant rapid and deep hematological response in patients with newly diagnosed AL amyloidosis along with an acceptable safety profile [12,17], especially in advanced cardiac stage (IIIa, IIIb) [12]
A risk-adapted and response-tailored approach, accounting for the patient characteristics, organ involvement and cardiac biomarkers is critical in the management of AL amyloidosis. The description of treatment patterns for AL amyloidosis patients and the assessment of survival and treatment outcomes in a real-world clinical setting are necessary to identify the trends and gaps in the standard of care.
Given the paucity of data on amyloidosis incidence, clinical and laboratory profile and treatment outcomes from India. Hence present study was aimed to study the clinical and laboratory profile along with the outcome in Indian patients with primary AL Amyloidosis.

2.Material & Methods

This was a retrospective observational study conducted at Sanjay Gandhi postgraduate institute of medical sciences, Lucknow, India in the department of hematology. Thirty-three (33) study subjects were added in to the study as per inclusion & exclusion criteria.
Inclusion criteria: All patients diagnosed with systemic amyloidosis as per guidelines were included in the study. The clinical and laboratory data of all the patients were retrieved from their electronic medical records from May 2007 till June 2018 and was further analysed.
Exclusion criteria: Patients diagnosed with other forms of amyloidosis (amyloid A [AA], transthyretin-related hereditary [TTR] amyloidosis, localized amyloidosis, or non-typification of the protein), were excluded from the study.
Statistical analysis: Descriptive statistics is presented as mean and standard deviation for continuous data and as numbers and proportions categorical data. Data analysis was done using IBM-SPSS statistics software ver. 23.0
Diagnosis of AL amyloidosis was confirmed by the presence of amyloid fibrils in the biopsy tissue by abdominal fat aspiration using Congo red staining, in addition to the demonstration of a monoclonal plasma cell proliferative disorder and the presence of amyloid-related systemic syndrome [19]. Renal amyloidosis was confirmed by light chain restriction by immunofluorescence and histopathological examination. Demonstration of plasma cell dyscrasia was demonstrated by measuring serum M protein through serum electrophoresis test. The electronic medical records include data for baseline demographics, medical history, comorbidities, physical examinations, laboratory, and imaging exams. Treatments were prescribed according to the hospital protocols.

3.RESULTS AND DISCUSSION:

In a study period from 2007 to 2018, thirty-three cases of primary amyloidosis were diagnosed according to the guidelines. Majority of cases belonged to 50-59 years age group (48.5%) followed by 40-49 years (21.2%), 60-69 years (18.2%) and 70-79 years (9.1%). 3% of patients belonged to >80 years. The male:female ratio was 1.5:1. All the patients had edema at presentation. Other most common signs & symptoms were pallor (45.5%) followed by breathlessness (30.3%), diarrhea (21.2%), weakness (18.2%), fever & cough (15.2%). On Laboratory investigations, Ultrasound showed hepatomegaly and splenomegaly in 12.1% of patients. 2D-Echo showed 15.2% cases with restrictive cardiomyopathy. The baseline clinical characteristics are shown in table 1.

Table 1: Demographic and clinical profile of patients at diagnosis

Parameters	Frequency	Percent
Age group		
40-49	7	21.2
50-59	16	48.5
60-69	6	18.2
70-79	3	9.1
>80	1	3.0
Sex		
Male	20	60.6
Female	13	39.4
Signs and symptoms		
Proteinuria (frothy urine)	33	100
Fever	5	15.2
Weakness	6	18.2
Joint pain	4	12.1
Bleeding episodes	3	9.1
Difficulty in swallowing	1	3.0
Diarrhoea	7	21.2
Paresthesia and numbness	3	9.1
Breathlessness	10	30.3
Cough	5	15.2
Nausea &vomiting	3	9.1
Edema	33	100
Pallor	15	45.5
Macroglossia	3	9.1
Petechiae or ecchymosis	1	3.0
Peripheral neuropathy or thickened peripheral nerves	3	9.1

Arrhythmia	1	3.0
Hepatomegaly	4	12.1
Splenomegaly	4	12.1
Restrictive cardiomyopathy	5	15.2

Out of 33 amyloid patients, M-Band was detected in 48.5% patients. Immunofixation results were negative in 48.5%. 10 patients (30.3%) were found with IgG Lambda type monoclonal protein followed by IgA Lambda type monoclonal protein & Lambda light chain type monoclonal protein in 9.1% each (table 2).

Table 2: Distribution of patients according to serum immunofixation

Serum Immunofixation	Frequency	Percent
Kappa light chain type monoclonal protein	1	3.0
IgA Lambda type monoclonal protein	3	9.1
IgG Lambda type monoclonal protein	10	30.3
Lambda light chain type monoclonal protein	3	9.1
Negative immunofixation	16	48.5
Total	**33**	**100.0**

All patients had renal involvement. Renal failure was observed in 42.4% patients. Cardiac plus renal involvement was found in 5 patients (15.2%) and 1(3%) patient had a GI (duodenum) involvement along with renal involvement. The 5 patients having cardiac involvement had Revised Mayo stage IV (table 3).

Table 3: Distribution according to organ involvement

Organ Involvement	**Frequency**	**Percent**
Renal involvement	27	81.8
Renal plus GI involvement (duodenum)	1	3.0
Renal plus Cardiac involvement	5	15.2

27.3% patients had received CyBORD (Bortezomib+cyclophosphamide+Dexamethasone) based regimen. None of the patients underwent autologous hematopoietic stem cell transplant either because of being transplant ineligible or due to financial constraints. Out of 33 patients, 13 (39.4%) were lost to follow-up. 11(33.3%) patients died. In this 1 patient died of cardiac arrhythmia and another with cardiac failure, 4 (12.1%) patients died of COVID-19 and 5 (15.2%) died due to gram negative septic shock. 9 (27.3%)

patients were alive. Among live patients, 1 was in complete remission , 1 was partial remission, 1 was stable, 2 patients were ESRD/dialysis dependent. 4 patients (12.1%) had progression of disease (table 4).

Table 4: Treatment and outcomes

Treatment received	Frequency	Perecent
CyBORD (Bortezomib+cyclophosphamide+Dexamethasone) based regimen	9	27.3
Autologous stem cell transplant	0	0
Deaths and cause		
COVID19	4	12.1
Gram negative Septic shock	5	15.2
Arrhythmia	1	3.0
Cardiac failure	1	3.0
Follow up		
Alive	9	27.3
Dead	11	33.3
Lost to follow up	13	39.4
CONDITION OF THE PATIENTS		
Complete response	1	3.0
Very good Partial response	1	3.0
Stable	1	3.0
Progression of disease	4	12.1
ESRD/dialysis dependent	2	6.0

In present study, majority of Primary amyloidosis cases belonged to 50-59 years age group (48.5%) followed by 40-49 years (21.2%) ,60-69 years (18.2%) and 70-79 years (9.1%). 3% of patients belonged to >80 years. Median age was 52 years. But in a study conducted by Sivaprakasam Y et al.,[20] median age was 59 years which was higher compared to present study.

All patients hadd Proteinuria on urinanalysis and had peripheral edema on clinical exam. Other most common signs & symptoms were pallor, breathlessness, diarrhea, weakness. Ultrasound showed hepatomegaly and splenomegaly in 12.1% of patients. 2D-Echo showed 15.2% cases with restrictive cardiomyopathy.

Out of 33 amyloid patients, immunofixation results were negative in 48.5%. 10 patients (30.3%) were found with IgG Lambda type monoclonal protein followed by IgA Lambda type monoclonal protein & Lambda light chain type monoclonal protein in 9.1%. 3% were found with kappa light chain type monoclonal protein. In a report by Sivaprakasam Y et al.,[20] Lambda monoclonal light chain was seen in 22/27 (81.5%) and kappa monoclonal light chain in 5/27 (18.5%) of patients.

In present study, all patients had renal involvement. Renal failure was observed in 42.4% patients. Cardiac plus renal involvement was found in 5 patients (15.2%) and GI plus renal involvement was found in 1 (3%) patient. These 5 patients of cardiac involvement had Revised Mayo stage IV. Six (18.2%) patients had more than one system involved while 27 (81.8%) patients had a single system involvement. Similar to this, previous studies have shown most common system involved was renal in 16 (59.2%), followed by cardiac in 13 (48.1%) and gastro-intestinal in 9 (33.3%). Fifteen (55.6%) had two or more system involvement while 12 (44.4%) had single system involvement.27.3% patients received CyBORD (Bortezomib+cyclophosphamide+Dexamethasone) based chemotherapy regimen. In a study by Sivaprakasam Y et al.,[20] fourteen patients were treated; cyclophosphamide, bortezomib and dexamethasone (CyBORD) in 10/14 (71.4%) and bortezomib + dexamethasone in 4/14 (28.6%). In the same study, among 14 patients followed up with median follow up of 13 months (range 6-60 months), 5 expired; 3 due to COVID, one due to cardiac arrhythmia (during first cycle) and one due to relapse and rest 9 were alive. Among the 9 patients who were alive 6 were in complete hematological response and 3 were in partial response after 6 cycles of therapy. Similar to these results, in present study 1 patient died with cardiac arrhythmia and another with cardiac failure, 4 patients died of COVID-19 and 5 patients died due to septic shock.

In present study, 9 (27.3%) patients were alive. Among live patients, 1 was in complete response, 1 in very good partial response, 1 was stable, 2 patients were ESRD/dialysis dependent. 4 patients (12.1%) had progression of disease.

4.CONCLUSION

This study highlights the importance of early diagnosis and treatment for patients with AL amyloidosis. It provides vital real-world evidence for the diagnosis and treatment outcomes for patients with AL amyloidosis in the Indian population, which would be useful for clinical decision making and help revolutionize the treatment for patients with AL amyloidosis. More real-world evidence data is required to further improve the patient care, and meet the unmet need, in terms of management of AL amyloidosis.

ETHICAL APPROVAL: Under review by Institute Ethics Committee (IEC). Waiver of consent has also been applied for to the IEC since this was a retrospective observational study.

REFERENCES:

1. Palladini G, Merlini G. What is new in diagnosis and management of light chain amyloidosis? *Blood*. 2016. Jul 14;128(2):159–68.

2. Zhang N, Cherepanov D, Romanus D, Kumar N, Hughes M, Faller D V. Estimating the Global Epidemiology of Amyloid Light-Chain Amyloidosis With an Incidence-to-Prevalence Model. *Clin Lymphoma Myeloma Leuk* 2019. Oct;19(10):e339.

3. Rosenzweig M, Landau H. Light chain (AL) amyloidosis: update on diagnosis and management. *J Hematol Oncol*. 2011. Dec 18;4(1):47.

4. Quock TP, Yan T, Chang E, Guthrie S, Broder MS. Epidemiology of AL amyloidosis: a real-world study using US claims data. *Blood Adv* . 2018. May 22;2(10):1046–53.

5. Aguirre MA, Boietti BR, Nucifora E, Sorroche PB, González Bernaldo de Quirós F, Giunta DH, et al. Incidence rate of amyloidosis in patients from a medical care program in Buenos Aires, Argentina: a prospective cohort. *Amyloid* . 2016. Jul 2;23(3):184–7.

6. Kyle R., Gertz M. Primary systemic amyloidosis: clinical and laboratory features in 474 cases. *Semin Hematol*. 1995;32(1):45–9.

7. Palladini G, Milani P, Merlini G. Novel strategies for the diagnosis and treatment of cardiac amyloidosis. *Expert Rev Cardiovasc Ther*. 2015;13(11):1195–211.

8. Palladini G, Merlini G. Current treatment of AL amyloidosis. *Haematologica*. 2009. Aug 1;94(8):1044–8.

9. EMA. European medicines agency. *Public summary of opinion on orphan designation; Chimeric fibril-reactive IgG1k monoclonal antibody 11-1F4 for the treatment of AL amyloidosis*. 2020.

10. AMC. *Guidance for Industry AL Amyloidosis—Developing Drugs for Treatment*. 2016.
11. Wechalekar AD, Gillmore JD, Bird J, Cavenagh J, Hawkins S, Kazmi M, et al. Guidelines on the management of AL amyloidosis. *Br J Haematol*. 2015. Jan;168(2):186–206.

12. Kastritis E, Palladini G, Minnema MC, Wechalekar AD, Jaccard A, Lee HC, et al. Daratumumab-Based Treatment for Immunoglobulin Light-Chain Amyloidosis. *N Engl J Med*. 2021. Jul 1;385(1):46–58.

13. Sanchorawala V, Skinner M, Quillen K, Finn KT, Doros G, Seldin DC. Long-term outcome of patients with AL amyloidosis treated with high-dose melphalan and stem-cell transplantation. *Blood*. 2007. Nov 15;110(10):3561–3.

14. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* [Internet]. 1982. Dec;5(6):649–55.

15. National Comprehensive Cancer Network. *NCCN clinical practice guidelines in oncology; Systemtic light chain amyloidosis*. 2013.

16. Skinner M, Anderson JJ, Simms R, Falk R, Wang M, Libbey CA, et al. Treatment of 100 patients with primary amyloidosis: A randomized trial of melphalan, prednisone, and colchicine versus colchicine only. *Am J Med* [Internet]. 1996. Mar;100(3):290–8.

17. Kastritis E, Leleu X, Arnulf B, Zamagni E, Cibeira MT, Kwok F, et al. Bortezomib, Melphalan, and Dexamethasone for Light-Chain Amyloidosis. *J Clin Oncol* [Internet]. 2020. Oct 1;38(28):3252–60.

18. Palladini G, Milani P, Foli A, Vidus Rosin M, Basset M, Lavatelli F, et al. Melphalan and dexamethasone with or without bortezomib in newly diagnosed AL amyloidosis: a matched case–control study on 174 patients. *Leukemia* [Internet]. 2014. Dec 25;28(12):2311–6.

19. Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos M-V, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol* [Internet]. 2014. Nov;15(12):e538–48.

20. Sivaprakasam Y, Kotwal J, Saraf A, Gupta P, Gupta N. clinical, laboratory profile, treatment and outcome of primary amyloidosis in the era of novel agents: an experience from a tertiary care hospital in india. hemasphere. 2022:3515-.