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A Quantitative Cross-Sectional Study Assessing the Prevalence and Distribution of Renal Amyloidosis Subtypes (AA and non-AA) in Biopsy-Proven Adult Cases

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ABSTRACT

Renal amyloidosis is a multisystem disease characterized by the deposition of misfolded proteins in various organs, leading to organ dysfunction. Renal amyloidosis subtypes vary across populations, depending on underlying conditions such as inflammatory diseases and plasma cell disorders. **Objectives:** To evaluate the prevalence and distribution of the different subtypes of renal amyloidosis. **Methods:** The sample for this quantitative, observational, cross-sectional study comprised 94 patients with biopsy-proven renal amyloidosis, aged 18 years or older, diagnosed during the period between January and December 2025. Renal biopsies were analyzed with the help of Congo red stain to confirm the amyloid deposition, and subtyping was done with the help of amyloid A (AA) immunostain. Cases with negative AA staining were classified as non-AA amyloidosis. **Results:** The most common subtype was AA amyloidosis (80%), followed by non-AA amyloidosis (20%). Males were 54.3 percent of the participants, while females were 45.7%. Mean age was 51.19 ± 20.45 years. There were no statistically significant gender differences in the distribution of amyloid subtypes or in biochemical parameters ($p>0.05$). **Conclusions:** The most common type of renal amyloidosis was AA amyloidosis, in which there were no significant gender-based differences in demographic or biochemical factors. The results are valuable to aid clinical planning and disease management.

INTRODUCTION

Renal amyloidosis is a constellation of aggressive protein-misfolding diseases characterized by extracellular insoluble amyloid fibrils in the kidney, leading to structural damage, progressive proteinuria, nephrotic syndrome, and eventual renal failure [1]. Systemic amyloidosis can be clinically heterogeneous, and the most prevalent forms of renal amyloidosis are AA amyloidosis and AL amyloidosis. More and more subtypes of amyloidosis are becoming familiar, including ALECT2 (leukocyte chemotactic factor 2) amyloidosis and ATTR (transthyretin) amyloidosis [2]. Amyloidosis is not a common disease, and therefore, the prevalence of amyloidosis worldwide has conventionally been low. Systemic amyloidosis, overall, is estimated to be approximately 30 cases per 100,000 people, with a median age of diagnosis in the mid-60s [3]. The most frequent systemic form, which in most cases involves the kidneys, is AL amyloidosis, whose incidence is estimated at 16.7 cases per million person-years, and prevalence is 69.0 per million

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adults in 2021 in the United States- one of the highest rates ever documented, probably due to improved detection and survival [4]. Traditionally, previous reports estimated the prevalence of AL at 30,000–45,000 cases in the United States and the European Union. Still, recent statistics indicate an escalating recognition and survival rate, so prevalence is on the rise [5]. Secondary to chronic inflammation, AA amyloidosis is also a well-known cause of renal amyloid deposition but is less common, with a historical incidence rate of about 12 cases per 1 million per year [6]. Modern data indicate that the incidence might be decreasing in developed countries, driven by advances in the treatment of chronic inflammatory diseases [7]. Nevertheless, in a cohort design based on renal biopsy, AA was found in most (61) cases of amyloidosis, with AL accounting for 19.5%, with a primary focus on regional variation and underlying disease burden on prevalence [8]. Besides the AL and AA types, other amyloid etiologies have surfaced, including leukocyte chemotactic factor 2 (ALECT2). ALECT2 is detected to be about 3 percent of all cases of amyloidosis worldwide, in large series (>4,000 cases), specifically more often in certain ethnic groups (e.g. Mexicans, South Asians, Punjabis, Native Americans and Egyptians). It is a major cause of renal amyloidosis in these groups [9]. There are significant socio-demographic trends of Amyloid diseases. In developed areas, AL amyloidosis is the most common form, which increases in prevalence with age, with an average age of diagnosis of the sixth and seventh decades of life, and with a small bias towards males [10]. Recent national death data in the United States indicate 8734 deaths related to renal amyloidosis annually, aged 22 and above with a decline in death rates up to 2016, after which the trend is reversing, and incurring a disproportionate burden on males, older adults, and Black/African Americans [11], in addition to highlighting expanding health disparities across geography and population. Geographic differences also indicate the presence of disease risk factors and the availability of diagnostics. In developing nations, AA amyloidosis is still important because of the chronic infection and inflammatory disorders, which lead to the increased biopsy prevalence in the given setting, as opposed to AL amyloidosis in developed countries [12]. Renal amyloidosis is associated with chronic inflammatory diseases (e.g., rheumatoid arthritis, infections) in the AA type, and with plasma cell dyscrasias (e.g., multiple myeloma and monoclonal gammopathy) in the AL type. Ethnic differences and genetic conditions contribute to the prevalence of certain subtypes, such as ALECT2, within particular groups. Renal amyloidosis is usually associated with heavy proteinuria, hypoalbuminemia, progressive renal dysfunction, and nephrotic syndrome clinically, negatively affecting prognosis in the case of no timely diagnosis and treatment [13].

Recent studies on renal amyloidosis subtypes with the use of immunohistochemistry have not been performed among the Pakistani population based on biopsy. The patterns of prevalence at the regional level are not known, and thus preventing proper diagnosis and specific treatment. The present research bridges that gap since it presents local information about the distribution. This study aims to determine the prevalence and distribution of renal amyloidosis subtypes (AA and non-AA) in biopsy-proven adult cases and to assess associated demographic and biochemical characteristics.

METHODS

The study was a quantitative, observational, cross-sectional study conducted at the Department of Pathology, Shaukat Khanum Memorial Cancer Hospital and Research Center, a tertiary-care referral center with specialized expertise in histopathology and renal pathology. The research was conducted from 1 January 2025 to 31 December 2025. It involved recruiting patients, collecting data, conducting laboratory testing, and analyzing results. An Institutional Review Board (IRB) of the Shaukat Khanum Memorial Cancer Hospital and Research Center reviewed and approved the study protocol before it started (Approval No: EX-26-08-23-01). A non-probability consecutive sampling method was utilized, in which all patients who met the eligibility criteria were included until the intended sample size was reached. The sample size was calculated using the formula: $n = Z2 \times p \times (1-p)/d2$. where Z = 1.96 (95% confidence interval), p = 10% (expected prevalence of renal amyloidosis based on prior biopsy-based studies), and d = 5% (margin of error). The minimum calculated sample size was 94 patients. Written informed consent was taken. The study included patients aged 18 years and above who had undergone renal biopsy and who had histopathological evidence of renal amyloidosis. The exclusion criteria included renal biopsies that did not contain glomeruli, tissue samples that were not well fixed, individuals who were known or treated cases of amyloidosis, along with those individuals who were recipients of renal transplantation. Retrospective data were collected from medical records, biopsy request forms, and clinical, laboratory, and epidemiological data. The variables collected were patient demographics (age, gender, residence), clinical history (chronic inflammatory or infectious diseases), and laboratory variables (serum creatinine, serum albumin, 24-hour urinary protein excretion). An automated biopsy gun (Bard MaxCore C, Bard Inc., Tempe, USA) was used to collect renal biopsy samples under real-time ultrasound guidance (Philips HD11 XE, Philips Healthcare, Amsterdam, Netherlands).

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Hematoxylin and eosin-stained slides of 4-5 microns thickness were prepared from formalin-fixed paraffin-embedded (FFPE) renal biopsy specimens. Congo red stain was done on all the biopsies for the confirmation of diagnosis, and amyloid A stain was done for typing and categorized as AA (Amyloid A-positive) and non-AA (Amyloid A-negative) amyloidosis. Immunofluorescence (IF) staining for κ (kappa) and λ (lambda) light chains or mass spectrometry-based proteomics, which could help in further subclassification, were not performed, as these methods were not available at the time of the study.

Data analysis was conducted using IBM SPSS Statistics version 26.0. Frequencies and percentages were used to describe the categorical variables, and the mean and standard deviation were used to describe the continuous variables. The histograms, skewness, and kurtosis values, and Kolmogorov Smirnov-test were employed to determine whether numeric variables were normal or not. The chi-square test was used to evaluate the association between categorical variables, and the independent-samples t-test was used to compare continuous variables when necessary. The p-value was taken to be statistically significant if less than 0.05.

RESULTS

The study sample comprised 94 participants, with a slightly larger number of males (54.3%) compared with females (45.7%). Most of the participants belonged to the rural population (54.3%). Cases of AA amyloidosis were 80.0%, and non-AA amyloidosis were 20.0%, Table 1.

Table 1: Socio-Demographic Characteristics and Renal Amyloidosis Types of Study Participants

Variables	Category	Frequency (%)
Gender	Male	51 (54.3%)
	Female	43 (45.7%)
Residence	Urban	43 (45.7%)
	Rural	51 (54.3%)
Amyloidosis Type	AA Amyloidosis	75 (80.0%)
	Non-AA Amyloidosis	19 (20.0%)

Respondents had an average age of 51.19 years, and the standard deviation of 20.45 years, which shows a wide age range. The laboratory findings demonstrated elevated mean serum creatinine and proteinuria, indicating significant renal involvement among the study participants, Table 2.

Table 2: Descriptive Statistics of Numeric Variables

Variables	Mean ± SD	95% CI Lower	95% CI Upper
Age (years)	51.19 ± 20.45	47.06	55.33
Serum Creatinine (mg/dL)	4.29 ± 1.89	3.91	4.67
Serum Albumin (g/dL)	3.21 ± 0.73	3.06	3.36
Proteinuria (g/day)	5.57 ± 2.78	5.01	6.14

Nearly half of the patients with AA amyloidosis 46 (49.33%) had no identifiable underlying disease at the time of diagnosis. Among known etiologies, tuberculosis was the most common association, followed by chronic inflammatory and rheumatologic disorders, Table 3.

Table 3: Underlying Diseases in Patients with AA Amyloidosis

Underlying Disease	Number of Patients (%)
Rheumatoid Arthritis	8 (8.00%)
Dermatopolymyositis	1 (1.33%)
Juvenile Idiopathic Arthritis	1 (1.33%)
Psoriatic Arthritis	1 (1.33%)
Tuberculosis	18 (18.67%)
Hodgkin Lymphoma	3 (2.67%)
Hepatitis	1 (1.33%)
Cystic Fibrosis	1 (1.33%)
Colitis	1 (1.33%)
Other Chronic Inflammatory Diseases	13 (13.33%)
Unknown Etiology	46 (49.33%)
Total	94 (100%)

The study compares the demographic and clinical characteristics of patients with AA amyloidosis (n=75) and non-AA amyloidosis (n=19). The mean age was slightly higher in patients with AA amyloidosis (52.36 ± 19.98 years) compared to those with non-AA amyloidosis (46.58 ± 22.15 years); however, this difference was not statistically significant (p=0.273). Similarly, no significant differences were observed between the two groups in terms of mean serum creatinine levels (4.05 ± 1.79 vs. 4.36 ± 2.19; p=0.525), serum albumin levels (3.23 ± 0.72 vs. 3.29 ± 0.68; p=0.765), or proteinuria levels (5.55 ± 2.64 vs. 6.07 ± 2.80; p=0.447). About gender distribution, males constituted a higher proportion of the AA amyloidosis group (49.3%) compared to the non-AA group (31.6%), while females were more frequent in the non-AA group (68.4% vs. 50.7%). However, this difference was also not statistically significant (p=0.203), Table 4.

Table 4: Comparison of Demographic and Clinical Variables between AA and non-AA amyloidosis

Variables	Non-AA, (n=19)	AA, (n=75)	p-value
	Mean ± SD, Frequency (%)		
Age (Years)	46.58 ± 22.15	52.36 ± 19.98	0.273
Serum Creatinine Level	4.36 ± 2.19	4.05 ± 1.79	0.525
Serum Albumin Level	3.29 ± 0.68	3.23 ± 0.722	0.765
Proteinuria Level	6.07 ± 2.80	5.55 ± 2.64	0.447
Male	6 (31.6%)	37 (49.3%)	0.203
Female	13 (68.4%)	38 (50.7%)	

DISCUSSION

The current study measured the socio-demographic distribution, prevalence of renal amyloidosis subtypes, selected biochemical parameters, and gender differences among patients with biopsy-proven renal amyloidosis. The

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subtype AA amyloidosis was more prevalent than non-AA amyloidosis in the current study population. This trend aligns with evidence from regional hospital studies in South Asia, where AA amyloidosis remains dominant because the prevalence of chronic inflammatory and infectious diseases remains high. For example, AA amyloidosis was found in 48% of cases of renal amyloidosis in a study (n=312), which is also very close to the figure in the current study alone [14]. On the national level, a renal biopsy registry study conducted in India (n=1250) reported a 52 percent prevalence of AA amyloidosis, a 28 percent prevalence of AL, and other types at 20 percent, with a slightly higher AA prevalence than in the present study [15]. Locally, evidence from the Middle East shows that AA prevalence ranges from 40 to 60 percent, depending on the burden of inflammatory diseases, corroborating the results of the present study [16]. Conversely, high-income populations, which are more globally connected, exhibit significantly higher rates of AL amyloidosis. A national study (n=30,000 cases) conducted in the United States estimated that AL amyloidosis accounted for 65.7% of systemic amyloidosis, and AA accounted for less than 10% of the latter, demonstrating improved management of chronic inflammatory diseases [17]. Therefore, the reduced percentage of non-AA amyloidosis in the current study indicates regional epidemiological variations rather than methodological discrepancies. The gender distribution of the study population was 54.3% males, and no statistically significant difference in the distribution of amyloidosis subtypes between genders was observed $\chi^2 = 0.214$, p=0.898). The same gender neutrality has been reported in a population-based cohort in France (n=1,006), where the distribution of amyloidosis subtypes did not differ significantly between females and males (p>0.05) [18]. On the other hand, elevated male dominance has been observed in most North American populations with AL amyloidosis, where 60-65% of cases were female [19]. The mean serum creatinine (4.29 ± 1.89 mg/dL), serum albumin (3.21 ± 0.73 g/dL), and proteinuria (5.57 ± 2.78 g/day) indicate significant renal impairment with severe protein loss and associated metabolic derangements in the study population. Nevertheless, Chi-square tests showed no significant association between gender and the categorized serum creatinine, albumin, or proteinuria (all p>0.05). Similar results were reported in a retrospective cohort study conducted in Egypt (n=210), which found no significant gender-based differences in the biochemical severity of renal amyloidosis [20].

The limitation of this study includes the unavailability of immunofluorescence (IF) staining for κ (kappa) and λ (lambda) light chains, as well as mass spectrometry, which prevented definitive subtyping of amyloid. Consequently, the non-AA cases could not be further classified into AL or other specific amyloid subtypes. Future research should incorporate IF and mass spectrometry–based proteomic analysis to enable accurate amyloid typing, improve diagnostic precision, guide targeted therapy, and enhance clinicopathological correlation through multicenter collaboration and improved resource availability.

CONCLUSIONS

This study highlights that AA amyloidosis is the predominant subtype of renal amyloidosis among adult patients in our population, reflecting the high prevalence of chronic inflammatory and infectious diseases in the region. The cases presented with severe renal involvement, with significant proteinuria and renal failure. There were no significant differences between male and female patients. The results offer valuable local epidemiological evidence and indicate the need for improved diagnostic facilities to perform further amyloid subtyping.

Authors' Contribution

Conceptualization: MH[1]
Methodology: MN
Formal analysis: MN
Writing and Drafting: MN, MH[1], UH, MH[2]
Review and Editing: MN, MH[1], UH, MH[2]

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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