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Original Research Article.

Pattern of Renal Involvement in Haematological Malignancy Patients Admitted in Dhaka Medical College & Hospital

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ABSTRACT

Background: Haematological malignancies are the most widely recognized nonrenal neoplasms influencing the kidney. The frequency and sort of renal association in these malignancies are variable and vary according to the type of malignancy.

Objective: To study the pattern of renal involvement in haematological malignancy.

Methods: This cross-sectional study was conducted in the department Nephrology, Haematology & Medicine in Dhaka Medical College and Hospital, from the December 2018 to the November 2019. A total of 96 patients with diagnosed case of haematological malignancies (leukemia, lymphoma and multiple myeloma) having clinical and laboratory evidence of renal involvement were included in this study. Informed written consent was obtained from the participants. Relevant investigations were done and kept recorded in a case-record form. Finally, statistical analysis of the results were obtained by using window based computer software device with Statistical Packages for Social Sciences (SPSS 22 windows 7 version).

Results: Mean age of all study subjects was 48.20 (± 12.88) years with male-female ratio 2.56:1. The most common type of hematological malignancy were multiple myeloma (36.5%) followed by leukaemia (33.3%) and lymphoma (30.2%). Majority of the patients had AKI (59.4%) followed by glomerulonephritis (21.9%) and CKD (18.8%). Among 19 patients of histologically proven glomerulonephritis secondary to haematological malignancy were found predominantly AL-Amyloidosis (12 patients) then membranoproliferative glomerulonephritis (5 patients) followed by minimal change disease (one patient) and membranous nephropathy (one patient).

Conclusion: In this study, renal involvement patterns were in the form of acute kidney injury, glomerulonephritis and chronic kidney disease. It was found that acute kidney injury may be the most common pattern of renal involvement in haematological malignancy.

Keywords: Multiple Myeloma, Leukaemia, Lymphoma, Acute Kidney Injury, Chronic Kidney Disease, Glomerulonephritis.

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INTRODUCTION

Haematological Malignancies (HM) are primary cancer which arises from the cells of bone marrow and lymphatic system[1]. The incidence of haematological malignancy is increasing day by day and are causing many deaths worldwide[2]. Although the prevalence of these malignancies are much lower in Asia and Africa than in Western countries but now a days the incidence of these malignancies are drastically increasing in low-income settings, while these increasing trends are not observed in Western countries[3]. The incidence of all cancer comprises approximately 6.5% worldwide. Information regarding

the epidemiological aspects of HM in Bangladeshi population is limited. The overall picture of cancer is unknown in this populous nation due to the nonexistence of population-based cancer registries. However, on the basis of GLOBOCAN estimate, age-standardized incidence rate (ASR) of hematological malignancies in Bangladesh is 2 per 100,000 which is relatively low as compared to the average ASR of low- and middle-income countries (4.5 per 100,000)[4,5].

Haematological malignancies are the most common non-renal malignancy affecting the kidney[6]. The renal complications of cancer have become one of the important determinants of prognosis in patients with malignancies and combined efforts of the hemato-oncologist and the nephrologist are required for care of these patients in a view of the wide spectrum of syndromes that may occur[7]. The renal complications of malignancies in addition to paraneoplastic glomerulopathy can occur either due to: a) mechanical (direct) effect of tumor in the form of infiltration of renal parenchyma, obstructive uropathy, compression of renal vessels b) metabolic (indirect) effects in the form of nephrocalcinosis, myeloma cast nephropathy, electrolyte disturbances, disseminated intravascular coagulation and thrombotic microangiopathy or c) treatment induced effects in the form of tumor lysis syndrome (TLS), lithiasis and uric acid nephropathy, radiation nephropathy, drug induced tubulointerstitial disease, thrombotic microangiopathy and mesangiolysis (Ronco 1999)[8]. These renal complications of haematological malignancies may be preventable or reversible with prompt diagnosis and treatment. But therapy induced renal involvement has been appearing as another important cause of renal failure. Tumor lysis syndrome which is an oncological crisis described by a mix of metabolic issue saw toward the beginning of treatment of hematological malignancies[10].

TLS might also be related with the advancement of aggressive lymphomas and leukemias. The syndrome is frequently associated with renal dysfunction. Renal failure occur after bone marrow transplantation for the treatment of selected haematological malignancy resulting from a variety of causes[10]. Early renal injury in most cases results from infection and its subsequent treatment. Bone marrow transplant (BMT) nephropathy refers to the late renal injury after bone marrow transplantation characterized by a syndrome similar to the hemolytic uremic syndrome.

Although many solid and haematological malignancies may involve the kidney, but the clinical sequelae are usually not prominent. Lymphomas, leukemias and multiple myeloma are most common cancers involving the kidney in many fashions. The association of nephrotic syndrome and malignancy is most striking in the patients with mixed cellularity type of hodgkin's diseases[11]. Proteinuria tends to reappear with relapse of lymphoma, supporting the statement that nephrotic syndrome is a consequence of malignant disease and not a coincidence[12].

Renal failure in multiple myeloma can be related to abnormal paraproteins, hypercalcemia, hyperuricemia, dehydration, the use of intravenous contrast agent, nephrotoxic drugs and many other factors.[13,14].

Renal involvement is relatively less common in leukemias and in some leukemias, renal impairment is usually found during the blastic crisis. Renal infiltration of leukemic cells has also been found in some patients. In addition, some types of haematological malignancies are associated with severe hypercalcemia that can lead to nephrocalcinosis. Considering the above facts, the study was designed to know the pattern of renal involvement in patients with haematological malignancies like lymphomas, leukemias and multiple myeloma admitted in Dhaka Medical College and Hospital.

METHODOLOGY

Study Design

Cross-sectional study

Study Place

Department of Nephrology, department of Haematology and department of Medicine, Dhaka Medical College and Hospital, Dhaka.

Study Period

December 2018- November 2019

Study Population

Diagnosed case of haematological malignancies (leukemia, lymphoma and multiple myeloma)

Sampling Technique

Purposive sampling

Study Procedure

The study was conducted in the department of Nephrology, Haematology and Medicine from December 2018 to November 2019 after taking ethical approval from ethical review committee of DMC. A total of 96 suspected renal involvement in the haematological malignancy patients presenting to the hospital were approached for participation of the study according to the inclusion and exclusion criteria. Three hematological malignancies including lymphoma (Hodgkin's disease and non-Hodgkin's lymphoma), Leukemia (acute and chronic leukemia's) and multiple myeloma patients were included. Prior known case of renal disease was considered as criteria of exclusion. The diagnosis was based on clinical findings, hematological findings and bone marrow examination or other relevant investigations. All leukemic patients were characterized as per FAB classification, whereas lymphoma patients were subdivided on histological basis (working formulation). The renal involvement was based on a detailed history, thorough physical examinations and necessary investigations. In all patients, urine routine microscopic examination, 24 hours Urinary Total Protein, blood urea, serum creatinine, CBC, serum electrolytes, serum calcium, serum phosphate, iPTH, serum uric acid and USG of KUB region were done. All the biochemical investigations were sent to the department of biochemistry and laboratory medicine, BSMMU where the tests were carried out by automated analyzer and ultrasonography was done from the nuclear medicine department of DMCH.

Data Collection

After selection of the patient aims, objectives and procedures of the study was explained with understandable language to the patient. Risks and benefits were also made clear to the patient. The patients were encouraged for voluntary participation, and they were allowed being free to withdraw themselves from the study. Then informed written consent was taken from each patient. A questionnaire was prepared considering demographic information's, relevant history, examination findings and investigation reports of all the study subjects. Any complication during the procedure and hospital admission was also recorded.

Data Collection Tools

Appropriate data were collected by using a preformed data collection sheet. These data were analyzed statistically by standard procedure to arrive at definitive conclusion in respect of the research questions.

Data Processing and Analysis

Data were collected, tabulated and analyzed statistically using an IBM personal computer and the statistical package SPSS version 22 (Chicago, Illinois, USA). Descriptive statistics were used to express the result. To express the continuous variables range, mean, and SD were used, whereas percentage (%) or frequency distribution were used to express categorical variables. Chi-square test was used to find out the association between two categorical variables. A level of P< 0.05 was considered statistically significant.

RESULTS

Total 96 patients with different haematological malignancies were included in this study. Mean age was 48.20 (± 12.88) years. Maximum and minimum age was 85 years and 22 years respectively. Majority of the patients were aged between 51-60 years (29.2%) followed by 22.9% in 41-50 years and 21.9% in 31-40 years group. Among 96 patients with haematological malignancy, 69 (71.9%) were male and 27 (28.1%) were female with male-female ratio 2.56:1. The most common type of haematological malignancy in our study was multiple myeloma (36.5%) followed by leukaemia (33.3%) and lymphoma (30.2%).

According to table 1, among leukaemia patients, majority were in 31-40 years group (37.5%) followed by 28.1% in 41-50 years age group. Mean age in leukaemia patients were 42.06±12.15 years. Among lymphoma cases, majority patients (44.8%) were in 51-60 years age group. Mean age was 47.31±12.84 years. Among Multiple myeloma patients, majority were found in 51-60 years group (34.3%) followed by 25.7% in 61-70 years group. Mean age was 54.54±10.76 years.

Regarding leukemia, most of the patients had equal distribution (31.25% of each type) of ALL, AML and CLL. 55.17% lymphoma patients were diagnosed as non-Hodgkin's lymphoma.

In each group of multiple myeloma, leukaemia and lymphoma, male predominance was seen clearly. According to table 4; we have 57 patients of AKI. Among them 10 AKI in AMI (17.57%), 8 AKI in ALL (14.03%), 10 AKI in CLL (17.57%), 8 AKI in HD (14.03%) and 7 AKI in NHL patients (12.28).

According to table 5, In our study, we have 21 patients with glomerulonephritis secondary to haematological malignancy. Among them 12 patients having GN with Multiple Myeloma, 4 patients having GN with Non-Hodgkin's lymphoma, 1 patient with Hodgkin's disease, 2 CML & 2 CLL patients having GN.

According to table 6, we have 18 patients with CKD. Among them 5 CKD patients found in Hodgkin's disease (27.77%), 4 CKD patients in Non-Hodgkin's Lymphoma (22.22%) and 9 CKD in Multiple Myeloma patients (50%).

Mean Hb level was reduced in all types of HM & there was a significant difference of Hb level in 3 types of HM where Hb% more reduced in leukemia. Mean s. creatinine & PTH was increased in all types of HM & there was no significant difference among them. Mean s. uric acid, blood urea & s. calcium level were found to be raised in all types of HM & there was a significant difference among them.

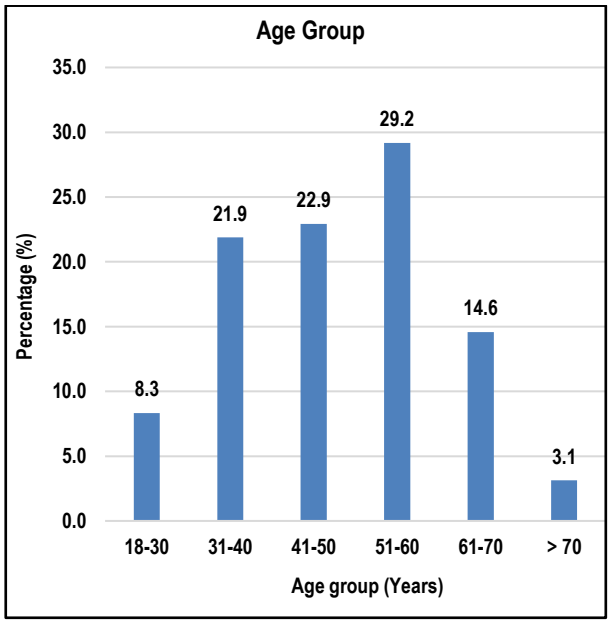

Figure 1: Distribution of study population according to age group (N=96)

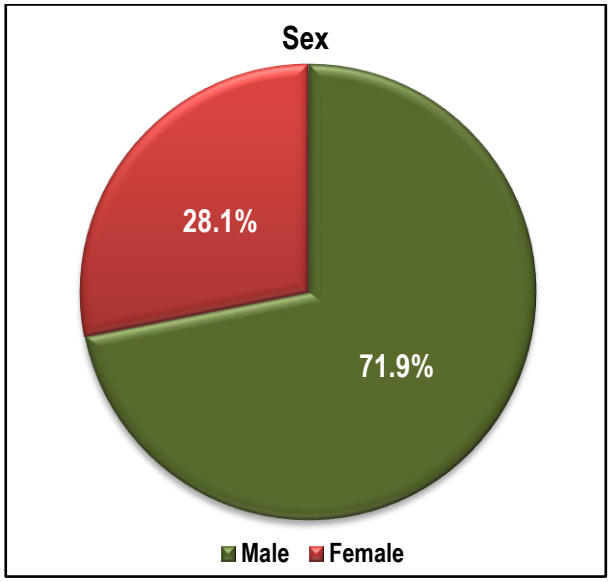

Figure 2: Sex distribution of study population (N=96)

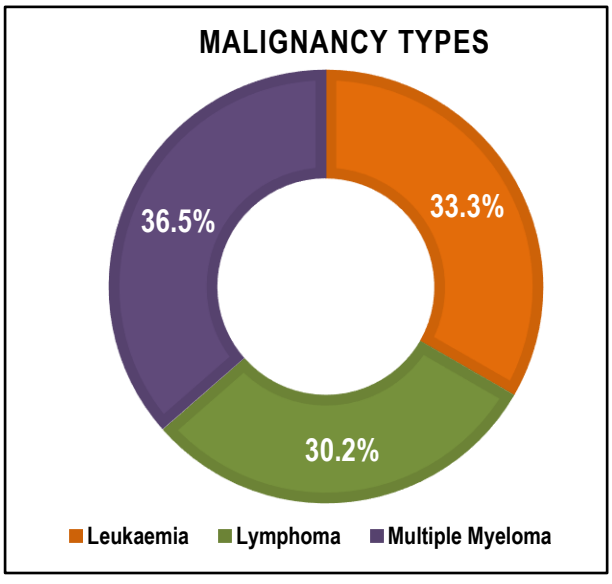

Figure 3: Major types of hematological malignancies (N=96)

Table I: Frequency of different types of haematological malignancy with renal involvement in different age group.

Age Group	Leukaemia N=32 n(%)	Lymphoma N=29 n(%)	Multiple Myeloma N=35 n(%)	P value
18-30 years	4 (12.5)	4 (13.8)	0 (0.0)	
31-40 years	12 (37.5)	5 (17.2)	4 (11.4)	
41-50 years	9 (28.1)	4 (13.8)	9 (25.7)	.010
51-60 years	3 (9.4)	13 (44.8)	12 (34.3)	
61-70 years	3 (9.4)	3 (10.3)	8 (22.9)	
> 70 years	1 (3.1)	0 (0.0)	2 (5.7)	
Mean age (years)	42.06±12.15	47.31±12.84	54.54±10.76	<0.001

Table II: Distribution of cases according to different types of haematological malignancy (N=96).

Malignancy	Male n(%)	Female n(%)	Total N(%)
Multiple Myeloma	**18(18.77)**	**17(17.72)**	**35(36.5)**
Lymphoma	**23(23.95)**	**6(6.24)**	**29(30.2)**
NHL	13(44.82)	3(10.34)	16(55.17)
Hodgkin's Disease	10(34.48)	3(10.34)	13(44.83)
Leukemia	**28(29.13)**	**4(4.26)**	**32(33.3)**
ALL	9(28.12)	1(3.12)	10(31.25)
AML	8(25)	2(6.25)	10(31.25)
CLL	9(28.12)	1(3.12)	10(31.25)
CML	2(6.25)	0	2(6.25)

*% out of total 96 patients

ALL: Acute lymphoblastic leukemia; AML: Acute myeloid leukemia; CML: Chronic myeloid leukemia; CLL: Chronic lymphocytic leukemia; NHL: Non-Hodgkin's lymphoma.

Table III: Clinical presentation of patients in different haematological malignancies with renal involvement (N=96).

Clinical presentation	Leukaemia (N=32) n(%)	Lymphoma (N=29) n(%)	Multiple myeloma (N=35) n(%)	P-value
Oliguria	24 (75.0)	24 (82.8)	18 (51.4)	**0.017^{S}**
Puffiness of face	29(90.6)	23 (79.3)	25 (71.4)	**0.142^{NS}**
Azotemia (nausea, vomiting, weakness etc.)	9 (28.1)	15 (51.7)	27 (77.1)	**<0.001^{S}**
Dark color urine	1(3.1)	5 (17.2)	7 (20.0)	**0.103^{NS}**
Proteinuria	4(11.4)	14(50.3)	21(77.2)	**<0.001^{S}**
Anaemia	32 (100)	24 (82.8)	31 (88.6)	**0.061^{NS}**
Weight loss	8 (25.0)	15 (51.7)	11 (31.4)	**0.077^{NS}**

Chi-square Test (χ^2) was performed to compare between groups; s= significant, ns= non-significant

Table IV: Number and frequency of AKI in Haematological Malignancy (N=57)

Types Of Haematological Malignancy	No. Of Patients with AKI n(%)
AML	10 (17.57)
ALL	8(14.03)
CLL	10(17.57)
HD	8(14.03)
NHL	7(12)
Multiple Myeloma	14(24.56)

ALL: Acute lymphoblastic leukemia; AML: Acute myeloid leukemia; CML: Chronic myeloid leukemia; CLL: Chronic lymphocytic leukemia; NHL: Non-Hodgkin's lymphoma; HD: Hodgkin's disease.

Table V: Number and frequency of Glomerulonephritis secondary to haematological malignancy (N=21)

Haematological Malignancy	Number of GN n(%)
Multiple Myeloma	12(57.14)
Non-Hodgkin's Lymphoma	4(19.09)
Hodgkin's Disease	1(4.76)
Chronic Myeloid Leukemia	2(9.52)
Chronic Lymphocytic Leukemia	2(9.52)

Table VI: Number and frequency of CKD in Haematological Malignancy (N=18)

Types Of Haematological Malignancy	No. Of Patient with CKD n(%)
Hodgkin's disease	5(27.7)
Non-Hodgkin's Lymphoma	4(22.22)
Multiple myeloma	9(50)

Table VII: Different investigation parameters in different haematological malignancy patients with renal involvement (N=96)

Investigation profile	Leukaemia (n=32)	Lymphoma (n=29)	Multiple myeloma (n=35)	P value
Hb% (gm/dL)	7.07±1.23	8.72±1.51*	7.63±1.62§	<0.001
Serum creatinine (mg/dL)	2.33±0.85	2.43±1.18	2.52±1.74	.846
Serum uric acid (mg/dL)	5.72±0.95	6.68±1.09*	6.52±1.36!§	.003
Blood Urea (mg/dL)	65.13±26.36	58.77±22.91	50.36±21.64!	.042
Serum Ca^{2+} (mg/dL)	9.34±0.32	8.68±1.31	11.39±2.50!§	<0.001
iPTH (pg/mL)	103.05±27.40	151.78±105.83	138.21±107.33	0.087

Values expressed as Mean±SD

Post hoc analysis with Bonferroni adjustment done.

* denotes the significant difference between leukemia vs lymphoma

!denotes the significant difference between leukemia vs multiple myeloma

§denotes the significant difference between lymphoma vs multiple myeloma

DISCUSSION

In order to know the pattern of renal complications in hematological malignancies, we conducted a study in nephrology department of DMCH.

Total 96 patients with different haematological malignancies were included in this study. Maximum and minimum age was 85 years and 22 years respectively. Mean age was 48.20 (± 12.88) years. Majority of the patients were aged between 51-60 years (29.2%) followed by 22.9% in 41-50 years group. As a whole 69.8% patients were in the age >40 years and 52.1% patients were aged between 41-60 years. Jung et al found ages between 60 and 69 were most prevalent followed by ages 70 to 79 and ages 50 to 59. Park et al found 63.9% patients presented in >50 years group in their study. Among leukaemia patients of our study, majority were in between 31-40 years group (37.5%) and as a whole 78.1% leukaemia patients in our study were aged <50 years. In lymphoma and myeloma patients, maximum aged between 51-60 years (44.8% and 34.3% respectively). Mean age in leukaemia, lymphoma and multiple myeloma was 42.06±12.15, 47.31±12.84 and 54.54±10.76 years respectively.

Haque et al found 40.15% of hematologic malignancies were between 41-60 year age group. Makkar et al found mean age of leukemia, lymphoma and multiple myeloma was 41.79±18.47, 47.30±21.30, 55.29±8.18 years respectively which was similar to my study. Among 96 patients with haematological malignancy, we have found 71.9 % were male and 28.1 % were female with male-female ratio 2.56: 1. Hossain et al found 5000 confirmed hematological cancer cases in Bangladesh and also found male predominance (69.2%) with male female ratio of 2.2:1. Egesie et al also found male predominance which is similar to us. It has been known that most myeloid and lymphoid are more common in males than females with a justification for this being that men are more likely to be exposed to potentially carcinogenic occupational and environmental agents.[15] The single most common presentation in all haematological malignancies was anaemia occurring 100% cases in leukaemia, 87.1% cases in lymphoma and 86.5% cases in multiple myeloma. The second most common presentations in leukaemia patients with renal involvement was puffiness of face (90.6%) while in lymphoma it was oliguria (82.8%) and puffy face (79.3%) respectively. In case of multiple myeloma, it was azotemia (77.1%) and puffy face (71.4%). It is consistent with the studies of Makkar et al who found 27.02% puffy face and oliguria in lymphoma,32.43% oliguria and puffy face in leukemia, 54.16% azotemia and 40.54% oliguria in multiple myeloma which were similar to this study[6].

In this study, mean serum haemoglobin was lowest in leukaemia patients 7.07±1.23 gm/dL while mean serum creatinine was 2.52±1.74mg/dl that was highest in multiple myeloma cases. Makkar et al. found in leukaemia as the lowest mean Hb% of 7.88 and in multiple myeloma to be the highest serum creatinine level of 4.66 mg/dl[6]. In this study, proteinuria was found in 39.6% cases. All patients presented with proteinuria Lower incidence of proteinuria in this study was probably because of less study population and their study included only those patients who had renal involvement in the form of proteinuria only.

In this study, about 13% patients were having dark color urine mostly in lymphoma and multiple myeloma. Pandit et al found 20% were having dark urine both in lymphoma and in multiple myeloma[7]. Out of 96 patients, 25% had hypercalcaemia. Among them, 68.5% were MM and 3.4% lymphoma. This study closely correlates with the study of *Burt et al.* in 1980 who reported that relatively high incidence of hypercalcaemia in haematological malignancies was found in multiple myeloma followed by lymphoma and leukemia[16]. Out of 32 acute leukaemic patients, a total of 6 (18.8%) patients had hypokalemia. Pandit et al found 20% patients had hypokelemia[7].

A total of 22 (22.9%) patients i.e. 4 (12.5%) in leukemia, 8 (27.6%) in lymphoma, and 10 (28.6%) in myeloma group had hyperkalemia. Pandit et al found hyperkalemia, 14.29% in lymphoma, 5.5% in leukemia and 30% in multiple myeloma[7].

We reported hyperphosphatemia in 25 (26%) patients in this study. Out of these, 1 had leukaemia, 13 lymphoma and 11 had multiple myeloma. Pandit et al found only one patient of multiple myeloma with hyperphosphatemia which is dissimilar with this study that may be due to more leukemia patients in their study where hypophosphatemia was more common.

Out of 96 patients, 32 (33.3%) had hyperuricemia which comprised 13 (37.9%) patients of lymphoma, 8(25%) patients of leukemia and 11 (37.1%) patients of multiple myeloma. Makkar et al found hyperuricemia, 48.4% in lymphoma, 51.1% in leukemia and 45.83% in multiple myeloma patients.

USG findings of hematological malignancy with renal involvement of this study showed 14.5% were having enlarged kidney with intact CMD, 13% patients with normal sized kidney and lost CMD, 6.25% were having contracted kidney with lost CMD and 66% were having normal findings. This study identified one case of HD with nephrotic range proteinuria and histological pattern revealed MCD. This study closely correlates with the study of KA Banday et al. (2004) who reported two patients with HD with nephrotic range proteinuria and histological pattern were MCD[17].

The study closely correlates with the study of Pandit et al. (2015) where they found CML with non-nephrotic proteinuria[7]. They also could not do renal biopsy due to bleeding manifestations and severe nature of illness. This study closely correlates with the study of R wanchoo et al. (2018) where they found CLL patient with glomerulonephritis having 36% MPGN and 19% MN[18]. They had studies among more than 50 cases. But in my study, I have found only 2 cases of CLL with GN. For this reason, percentage of glomerular involvement may be dissimilar.

In this study, there were 12 patients with multiple myeloma having GN with subnephrotic range proteinuria with renal impairment. Histological pattern of all 12 cases revealed AL amyloidosis. These dissimilarities may be due to less number of cases. Park and coworkers reported a case of fibrillary GN in a known case of multiple myeloma. Mcleish and colleagues reported a case of mesangial proliferative GN in a known case of MM. Sethi and coworkers reviewed renal biopsies of MPGN patients at Mayo clinic, Monoclonal gummopathy of unknown significance was the most common cause. Shah and colleagues reported a case of primary FSGS and smoldering MM. Crosthwaite and coworkers reported a case of rapidly progressive GN following amyloidosis. Different pattern of GN was seen in multiple myeloma which was dissimilar with our study. These dissimilarities may be due to less number of cases and also may be due to short duration of study.

CONCLUSION

In this study, renal involvement patterns were in the form of acute kidney injury, glomerulonephritis, and chronic kidney disease. It was found that acute kidney injury may be the most common pattern of renal involvement in haematological malignancy.

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