CLINICAL PROFILE AND OUTCOME OF PATIENTS WITH CLINICAL DIAGNOSIS OF RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS: A RETROSPECTIVE STUDY AT TIKUR ANBESSA SPECIALIZED HOSPITAL, ETHIOPIA

Principal Investigator: Beka Aberra Deressa, MD, Internist, Nephrology Fellow

Reg. No: GSR/1892/14

A Thesis to be submitted to the Department of Internal Medicine, School of Medicine, College of Health Sciences, Addis Ababa University for partial fulfillment of the Sub-Specialty Certificate program in Nephrology.

December 2023

Addis Ababa, Ethiopia

CLINICAL PROFILE AND OUTCOME OF PATIENTS WITH CLINICAL DIAGNOSIS OF RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS: A RETROSPECTIVE STUDY AT TIKUR ANBESSA SPECIALIZED HOSPITAL, ETHIOPIA

Principal Investigator: Beka Aberra, MD, Internist, Nephrology Fellow

Mobile Number: +251911037092

Email: bekaaberra@aau.edu.et

Advisor: Addisu Melkie, MD

Consultant Internist & Nephrology Sub-Specialist

Signature: _____

Department Head: Amsalu Bitew, MD

Consultant Internist & Pulmonary & Critical Care Sub-Specialist

Signature: _____

December 2023

Addis Ababa, Ethiopia

ACKNOWLEDGEMENT

I want to express my deepest gratitude to Jesus Christ for His abundant blessings, unwavering support, and immeasurable mercy throughout the course of this research. Without His divine guidance, none of this would have been possible.

I would, also like to extend my sincere appreciation to Addis Ababa University, College of Health Science, and specifically the Department of Internal Medicine and Nephrology unit, for providing me with the opportunity to conduct this research. The resources, facilities, and intellectual environment offered by the institution have been instrumental in the successful completion of this study.

I am especially grateful to my advisor, Dr. Addisu Melkie, for his invaluable expertise, continuous guidance, and unwavering commitment throughout the entire research process. His insightful comments, constructive criticism, and dedication to my academic and personal growth have played a pivotal role in shaping this study. I am truly fortunate to have had him as my advisor.

Finally, yet importantly, I am deeply thankful to my wife and my family for their unwavering love, understanding, and encouragement. Their constant support and belief in me have been a source of inspiration and motivation throughout this research endeavor.

Thank you all for your invaluable contributions to this project.

LIST OF TABLES

LIST OF FIGURES

LIST OF ANNEX

Table of Contents Pages

ACRONYMS AND ABBREVIATIONS

ANCA ……. Ant neutrophil cytoplasmic antibody

Anti-GBM ……. Anti-glomerular basement membrane

C3 ……. Complement component 3

C4 ……. Complement component 4

CBC ……. Complete blood count

CI ……. Confidence interval

CKD ……. Chronic Kidney disease

CRP ……. C-reactive protein

EMR …….Electronic Medical Recording

eGFR…….Estimation of Glomerular Filtration Rate

ESR ……. Erythrocyte sedimentation rate

ESRD ……. End-stage renal disease

GFR ……. Glomerular filtration rate

HR ……. Hazard ratio

IgA ……. Immunoglobulin A

IgG ……. Immunoglobulin G

IQR ……. Inter-Quartile range

KM ……. Kaplan Meier

MMF…… Mycophenolate Mofetil

OR ……. Odds ratio

PICT ……. Provider-initiated counseling and testing

PSGN …….Post streptococcal glomerulonephritis

RPGN ……. Rapidly progressive glomerulonephritis

SPSS ……. Statistical Package for the Social Sciences

URT…….Upper Respiratory Tract

ABSTRACT

Background: Rapidly progressive glomerulonephritis (RPGN) is a clinical syndrome defined by the rapid loss of renal function, accompanied by features of the nephritic syndrome with proteinuria, glomerular hematuria, and often oliguria. Early recognition and prompt diagnosis and treatment are crucial to prevent irreversible loss of renal function due to the limited availability of renal histopathology services.

Objective: To assess the clinical profile, efficacy, and safety outcome of immunosuppressive therapy and determinants of outcomes in patients with clinically diagnosed Rapidly Progressive Glomerulonephritis who were on follow-up at Tikur Anbessa Specialized Hospital in Ethiopia.

Methods: This retrospective study was conducted among all patients who fulfilled the clinical criteria of RGPN who were managed in the hospital from January 1st, 2016 to January 31st, 2023 with at least six months of follow-up. Patient characteristics were presented using frequencies with percentages, mean ± standard deviation (SD) or median with Interquartile range (IQR) values, and graphs. Efficacy was assessed using the proportion of patients with decreased serum creatinine from baseline or stabilization of serum creatinine. Lack of response was evaluated as an increase in serum creatinine from baseline, requirement or dependence on renal replacement therapy or death from renal cause. Safety was assessed using the proportion of patients with documented infections, hospitalizations for infection, or death from documented infections. Comparison of infection rate and patient outcome was made using Chi-square, independent t-test/ Mann-Whitney U-test, one-way ANOVA, and their non-parametric correlates when assumptions of the tests failed.

Results: The median age of the participants was 37 years (IQR, 25.0-51.5 years) and 25/45 were females. The most common comorbid illness was hypertension (13/45). The median duration of illness was 14.0 days (IQR, 9.5-28.0 days) and the most frequent presenting symptoms were oliguria (35/45) and extra-renal symptoms of respiratory (22/45) like pulmonary (13/45), upper respiratory tract (9/45), and rheumatologic (9/45) systems. The most common treatment complications were infection (15/45) and hematologic complications (4/45). Renal treatment response was documented at 12 and 24 weeks for 22 and 23 patients, respectively. The majority (20 patients) showed a significant decrease in Cr, three patients experienced stabilization of Cr levels, and the remaining two patients showed a progressive increase in Cr levels. Furthermore,

from the 45 patients, complete follow-up was made for 34 patients and the remaining 11 patients were lost to follow-up. From the 34 who were followed at the hospital, 12 achieved complete recovery, eight achieved partial remission, and six cases progressed. Of those who progressed, four developed CKD, and two progressed to ESRD. The rest eight patients died.

Conclusion and Recommendation: Clinically suspected RPGN patients in this study had little histologic diagnosis; and high remission rates with more infections on Immunosuppressive. We recommend the initiation of timely immunosuppressive treatment for those with Crescentric RPGN and de-escalating immunosuppression for those with benign diseases.

Keywords: Clinical Rapidly Progressive Glomerulonephritis, renal recovery, patient outcome, Ethiopia

INTRODUCTION

1.1. Background

Rapidly progressive glomerulonephritis is an acute nephritic syndrome accompanied by glomerular crescent formation with progression to renal failure within weeks to months [1,2]. RPGN is relatively uncommon, affecting 10 to 15% of patients with glomerulonephritis, and occurs predominantly in patients 20 to 50 years [1, 3].

Manifestations can be renal or extra-renal affecting different body systems and are usually insidious. In some patients, it is reported that the presentation can be sudden with most presenting with an abrupt-onset hematuria. About 50% of patients have edema and a history of an acute influenza-like illness within 4 weeks of onset of renal failure, usually followed by severe oliguria. Nephrotic syndrome is present in 10 to 30% of patients [4, 5].

Various etiologies lead to RPGN, including anti-glomerular basement membrane (GBM) antibody disease, immune complex deposition glomerulonephritis, and pauci-immune diseases associated with Antineutrophil cytoplasmic antibody (ANCA) [6,7]. Diagnosis is based on history, urinalysis, serologic tests, and renal biopsy [8, 9].

The mainstay of treatment is with corticosteroids, with or without cyclophosphamide or rituxima b, and sometimes plasma exchange. Dialysis is also provided as an initial management or maintenance depending on the severity of the situation. In untreated cases, spontaneous remission rarely occurs, and 80 to 90% progress to end-stage renal disease within 6 months. Early diagnosis and treatment improve renal and patient survival [10-13].

1.2.Statement of the problem

So far, RPGN is reported to be relatively uncommon in many parts of the world despite the diagnostic challenge in resource-limited settings. In studies that included cohorts of patients who were followed for up to 25 years, a prevalence as low as 1.56% to as high as 15% based on biopsy-proven results were reported. This could be attributed to the ever-changing lifestyle and increased life expectancy, both of which are well-known contributors to a variety of chronic medical illnesses in the modern era. It could also be due to technological advancement, which is associated with increased diagnostic capacity, increased care seeking, and access to care in the

majority of settings all of which require further study and understanding of the disease burden, prognosis, and outcome [1, 3, 14].

Although uncommon, it is a life-threatening syndrome with a risk of renal failure that requires dialysis in up to 30% of patients and could result in death in a significant proportion. As a result, early detection, diagnosis, and treatment are critical to preventing irreversible renal function loss and death [8-10].

The definitive diagnosis of RPGN requires pathologic evaluation; however, due to insufficient infrastructure, diagnosis in developing countries is primarily based on clinical parameters. In Ethiopia too, diagnosis is primarily based on clinical manifestation, due to a lack of pathologic assessment in the country, patient biopsy specimens must be sent abroad. Most patients cannot afford this, so the diagnosis is made solely on clinical presentation. In addition, for those who can afford it, the results can take up to a month and a half, where the most critical part of the decision is hampered. The Access for a Biopsy, The Cost of Investigation, and The Time of getting the results are the challenges in managing RPGN in Low resource setup. Therefore, presuming possible reversibility in patients clinically suspected of RPGN where rapidly rising creatinine is observed or initial presentation of an already high creatinine at presentation, clinicians need to make timely decisions. So after ruling out infections, endocarditis, and patients having a short symptom duration, with active urinary sediments and normal kidney size, patients are empirically started on immunosuppression. So questions arise about the outcomes, treatment-related complications, and over-treating our clinically suspected RPGN patients.

1.3. Justification of the study

Due to the relatively rare nature of the disease condition and the diagnostic challenge associated with it, evidence on RPGN is limited, particularly in developing countries. Ethiopia is one of the countries with this limitation, where initiation of treatment is primarily based on clinical diagnosis with later pathologic confirmation whenever possible. Therefore, understanding the clinical pattern of the disease in our setup will help us identify the typical clinical presentation of RPGN and hence can be used to guide the clinical diagnoses and will play a critical role in avoiding under and over-treatment of these groups of patients.

1.4. Significant of the study

The study's findings can be used to guide practitioners and decision-makers in the field at the regional and national levels who are involved in patient care and/or guideline development. Furthermore, it serves as a baseline study to understand the disease burden, presentation, and clinical diagnostic accuracy, which can then be used to design a large multicenter study in the country for better evidence.

2. LITERATURE REVIEW

2.1.Epidemiology and Clinical Profile of RPGN

RPGN is reported to be a very rare disease worldwide. The incidence varies with geographical and personal characteristics disparity implying the possible role of environmental factors in addition to personal attributes. An incidence of 7 cases per 1 million person per year is reported in the United States. While in the UK and Sweden, a proportion of 2 and 1 cases per 100,000 persons is reported. Regarding race, white people are more frequently affected compared to Asians and blacks, where the latter race is the least affected. In the United States, a ratio of as high as 7:1 is reported. However, RPGN is revealed to have a bad prognosis among blacks [15,16].

RPGN is a disease that affects both sexes at approximately comparable proportions and all ages. Studies show that, even though the disease affects all ages, it is very rare in pediatric age groups and it has a bimodal peak where the mean age for clinical manifestation is reported to be 30 years and 60-70 years [17,18].

The epidemiologic distribution of RPGN based on the three types showed that anti-glomerular basement membrane (GBM) disease constitutes 10 to 15% of cases, with an incidence of 0.5-0.9/million/year. This type is reported predominantly among whites and it shows a slight male predominance of 3:2 ratio. The second type, immune complex glomerulonephritis comprises 25 to 30% of all cases. The third type, pauci-immune type, is reported to be the most common type of crescentic glomerulonephritis accounting for 65 to 75% of histopathological reports in patients clinically diagnosed to have RPGN. This type is mainly reported in white patients and the peak age for diagnosis is 60 to 85 years. This type is typically associated with Antineutrophil cytoplasmic antibody (ANCA), which has been reported in more than half, 57.5% up to 63.9%, of patients with pauci-immune RPGN [14,19-21].

Symptom presentation differs depending on the type of RPGN and other personal factors. The majority present with a rapid decline in renal function over weeks to months, with most presenting with non-specific symptoms during the early stages. In the presence of other underlying conditions patients present with extra-renal symptoms that might cause diagnostic dilemmas and delays, especially in setups where there is limited infrastructure for adequate diagnosis [21]. Among patients with anti-GBM disease, presentation is mainly pulmonary due to

diffuse alveolar hemorrhage that results in shortness of breath, cough, and hemoptysis in addition to renal symptoms and signs including nephritis, hematuria, and edema [22]. The presence of extra renal symptoms is an indication of the presence of immune complex disorders or ANCA vasculitis. These features could range from constitutional symptoms like fever, night sweats, weight loss, and arthralgia to specific system manifestations that could include ophthalmologic, respiratory, gastrointestinal, central nervous system, and dermatologic signs and symptoms. In cases of delayed diagnosis and management that resulted in further progression of renal damage, renal failure Is eminent. Patients who are at the stage of renal failure present with features of renal and systemic symptoms that result due to accumulation of nitrogenous waste products including fatigue, loss of appetite, nausea, and vomiting, decreased urine output, and edema [19-22].

The nature of the onset of symptoms influences these patients' health-care-seeking behavior. According to studies, the average duration of symptoms can range from one week in those with an abrupt onset disease to more than two years in those with an insidious onset [21,25]. According to a study conducted in the United Kingdom, the most common extrarenal organ involved was the lung (63%), followed by the nose/sinuses (50%), joints (42%), muscle (33%), skin (22%), and the nervous system (14%). Furthermore, 47% of patients were diagnosed with hypertension [25].

Studies conducted in Africa also proved that RPGN is a rare condition but it is more prevalent than what other countries have reported so far. A study conducted in Nigeria reported a 1.9% prevalence of RPGN. On the other hand, studies conducted in South Africa and Senegal showed prevalence of 4.38% and 5.33%, respectively. Furthermore, the age distribution also showed that RPGN is a disease of the young in an African population. These studies reported a mean age of diagnosis of 30.7 to 33.9 years. In addition, RPGN among children was reported from Zambia where these children were diagnosed with crescentic glomerulonephritis after presenting with rising serum creatinine, hypertension, and hematuria. Concerning sex distribution, although a large-scale systematic review and meta-analysis reports in Africa showed that RPGN does not predominantly affect one sex, a clear female predominance, up to three-fold, was recorded in Africa [26-29].

The clinical profile of patients in Africa revealed that the frequent presenting symptoms are oliguria/anuria, rising serum creatinine and urea, proteinuria, and hematuria. In addition, late presentation with renal insufficiency was reported in a significant proportion. Immune complex-mediated RPGN was reported in majority [26,28-29].

2.2. Diagnosis and treatment

The diagnosis of RPGN is made based on clinical presentation together with laboratory tests, to confirm the presence of major causes of RPGN, and pathologic confirmation. The frequent findings that show the level of renal damage include the presence of microscopic hematuria and proteinuria of different degrees on urinalysis and findings of elevated serum creatinine and abnormal electrolytes on blood samples. To identify the types of RPGN and the presence of underlying causes, serologic tests are key. Although serologic tests are key in the diagnostic process, renal biopsy is still the gold standard as the sensitivity of these tests can be low. It is demonstrated that close to 10% of patients who have anti-GBM diagnosis through kidney biopsy were reported to have no identifiable circulating antibodies with serologic tests [30].

Due to its progressive nature, RPGN should be treated early to prevent further damage to the kidney that could result in renal failure and mortality. Hence, empiric treatment should be initiated, even before a definitive diagnosis is reached, based on clinical and readily available laboratory test results [31]. The empiric therapy includes a pulse IV dose of methylprednisolone, either 500 mg or 1 gm, for a minimum of 3 doses. Plasmapheresis may be considered specifically if the patient has hemoptysis raising concern for the severe form of Goodpasture's disease until it is confirmed. Once a definitive diagnosis is made, therapy should be targeted based on the specific type of RPGN. In most cases, immunosuppressive therapy, with glucocorticoid or cyclophosphamide, together with plasmapheresis is the treatment of choice. Further treatment of underlying conditions and their etiology should be followed according to the diagnosis made [32-35].

2.3. Treatment outcomes and predictors

Treatment response can range from complete remission (5.4% to 10.9%) to partial remission (25-45%). Upon diagnosis, up to 59% of patients may require dialysis. After receiving additional immunosuppressive therapy, 36.0 -48.0% of patients may require long-term dialysis. Progression

to ESRD has been reported in one-third of patients, but it may be as high as two-thirds when the ANCA-associated pauci-immune type is present [24-25, 38-40]. A study conducted in Africa also reported that following immunosuppressive treatment using a combination of corticosteroids and cytotoxic drugs, recovery was achieved in 18.2% of patients and 72.7% of patients progressed to chronic kidney disease [28].

According to studies that compared ANCA-positive and negative pauci-immune RPGN, ANCA-positive patients are mostly young patients who have high proteinuria, increased nephrotic syndrome, prominent airway symptoms, multiorgan involvement with a histologic feature of fibrinoid necrosis, and are at a higher risk of progression to end-stage renal disease (ESRD) and poor renal survival. Patients with ANCA-negative pauci-immune RPGN, on the other hand, have been reported to have a significantly higher proportion of extra-renal system involvement and to be diagnosed earlier, which could be attributed to their multi-system presentation [23-25, 36-37].

Patient survival is reported to differ depending on the patient's characteristics and the type of RPGN. As a result, a one-year mortality rate of 8.2% to 23.0%, a two-year mortality rate of 31.2%, and a five-year mortality rate of up to 40% are reported [15-17, 30-31]. Renal survival rates have also been reported to range between 44.3% and 82.0% [25, 40, 43].

Renal and patient survival is attributed to various factors including patient characteristics, pre-treatment renal status, and type of histopathologic lesions [20]. On histopathologic assessment, the extent of crescentic involvement on microscopic findings is indicative of the prognosis. Usually, a focal lesion with more than 50% normal glomeruli has a more favorable prognosis, almost 90% or more renal survival after 5 years follow up after treatment. Whereas more than 50% of glomeruli with cellular crescent have a less favorable prognosis of around 75% renal recovery at 5 years follow up. When more than 50% of glomeruli are globally sclerosed, the 5-year renal recovery is less than 25%. The extent of chronic tubule-interstitial fibrosis lesions can also affect the prognosis. In addition, the disruption of Bowman's capsule is associated with poor outcomes [39, 44, 47].

From personal characteristics, only age is ascribed to be associated with treatment outcomes. Younger patients are reported to respond well to treatment although the overall prognosis might

not differ significantly as compared to older patients. About gender, it was found that prognosis does not seem to have a significant difference between males and females [23-24, 44].

High proteinuria has not been shown to affect short-term prognosis but having a persistently high proteinuria following treatment is associated with poor long-term outcome in terms of both renal and patient survival [36, 44].

Baseline renal function is another predictor of treatment outcome. Anuria, low eGFR, high serum creatinine, and the need for initial and maintenance dialysis are found to be associated with poor outcomes after the treatment and progression to renal failure [43-44, 46-48].

Baseline antibody level also affects the prognosis, specifically a higher anti-GBM Ab level at the time of diagnosis is associated with the poor renal outcome, and ANCA positivity in general is associated with poor renal outcome [40, 42-44].

It is also found that the DRB 1* 15 allele is a risk factor for Anti-PR3 ANCA vasculitis. HLA DR-2 and/or B-7 have a possible association with the severity of the disease and the outcome [45].

Furthermore, patients who have additional systemic conditions like hypertension and pulmonary hemorrhage were found to have an increased risk of progression to renal failure. On the other hand, RPGN associated with drugs and infection is found to be associated with a better outcome [24-25, 36].

The above predictors of treatment outcome are also in line with a study conducted in Africa. In this study where a recovery rate of 18.2% was achieved, Poor renal outcome was predicted by having oligo anuria, high creatinine level upon admission, use of hemodialysis, and evidence of fibro-cellular and fibrous crescents [28].

Moreover, secondary complications following RPGN are a common occurrence given the potential for a multisystem presentation or due to disease progression. In one study conducted in India, secondary complications such as anemia and infection were reported in 90.0% and 67.0% of the patients, respectively [38].

2.4.Current practice and challenges in Ethiopia

As explained above, due to limited diagnostic facilities and associated costs, nephrologists in Ethiopia are faced with decisions on whether to give immune suppressive therapy or not to patients with clinical RPGN. These are patients that are labeled to have clinical glomerulonephritis (nephritic syndrome or predominately nephritic syndrome) and progressively declining GFR, normal or increased kidney sizes on ultrasonography with no evidence of active or recent infections. Leaving these patients untreated might result in rapid progression to end-stage kidney disease and loss of the window of opportunity to treat. Treating with potential toxic immunosuppressive therapy without having histopathologic evidence of activity/chronicity and specific diagnosis might put some patients at an increased risk of treatment-related toxicity.

In our current practice, when we are faced with a patient having a clinical syndrome of RPGN, we do the following;

1. To ascertain the patient has the full clinical picture as indicated by the following presentations;

The presence of glomerular proteinuria and hematuria (proteinuria above 1000 mg in 24 hours with hematuria), progressively rising serum creatinine, oliguria, and edematous state with or without high blood pressure will be considered to have the clinical syndrome of RPGN.

2. Trying to exclude chronic glomerular disease through history and ultrasound as follows;

History: The duration of illness will be assessed using history, baseline serum creatinine (if there is any)

Ultrasound of the kidneys: all patients will be subjected to at least one ultrasound study confirming normal or increased kidney sizes.

3. Excluding common infectious etiologies

All patients will have HBsAg, HCVAb, HIV tests, and VRDL/RPR tests

If there is a history suggestive of preceding upper respiratory tract or skin infection, ASO titer will be done

Echocardiography will be done if there is a clinical suspicion of infection

4. Doing readily available serologic tests

Almost all patients will have a qualitative ANA test if they can afford to do it.

5. Ascertaining the progressive or non-self-limiting nature of the disease

Patients with decreasing or plateauing serum creatinine will be observed with immunosuppressive treatment

6. Doing further etiologic work, for patients who can afford that

C3 and C4 levels

Quantitative ANA and anti-dsDNA

ANCA (MP0-ANCA and PR3-ANCA)

Anti-GBM antibody

7. Finally, patients will be offered to do a kidney biopsy

The decision to give immunosuppressive therapy is made if criteria 1-5 are fulfilled.

2.1. Conceptual framework

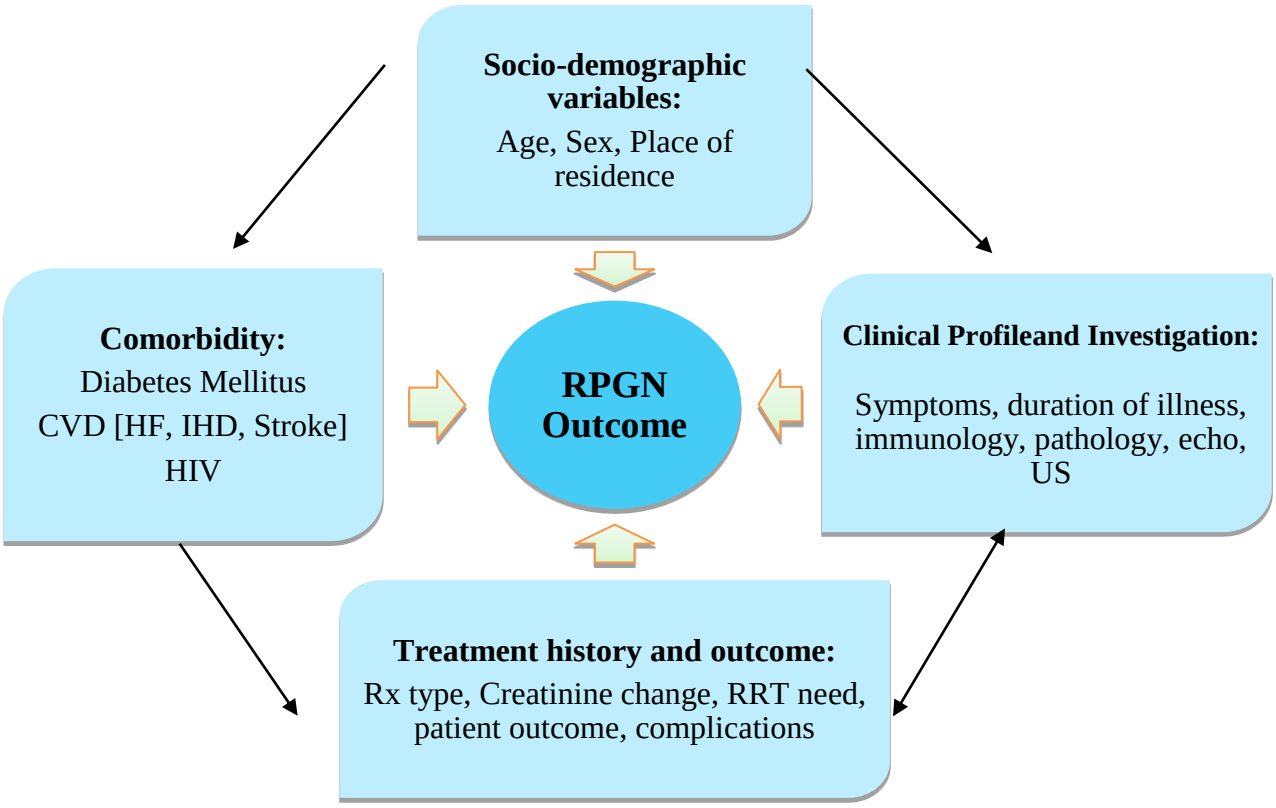

Figure 1: Conceptual framework of predictors of treatment outcome among patients with RPGN developed by the investigator based on literature, 2023 (3-5, 7-12).

3. OBJECTIVES

3.1. General objective

- To assess the clinical profile and outcome of patients with clinically suspected Rapidly Progressive Glomerulonephritis (RPGN) who were on follow-up at Tikur Anbessa Specialized Hospital (TASH) in Ethiopia from January 1st, 2016 to January 31st, 2023.

3.2. Specific objective

- To characterize the clinical profile of patients with clinically suspected RPGN who were on follow-up at TASH
- To determine treatment outcomes of patients with clinically suspected RPGN who were on follow-up at TASH

4. METHODS AND MATERIALS

4.1. Study setting and period

The study was conducted from May 15th to October 15th, 2023 at Tikur Anbessa Specialized Hospital (TASH), a teaching hospital under the administration of Addis Ababa University in Ethiopia. The hospital was established in 1972 as the teaching hospital of Addis Ababa University, College of Health Sciences. It is the largest referral hospital in the country with 700 in-patient beds and 12 ICU Beds as well as several outpatient referral clinics. The nephrology unit was officially established 20 years back and it has a total of 10 in-patient beds and 03 dialysis machines and has an average of 300-400 patients in three referral clinics monthly.

4.2.Study Design

The study employed a retrospective cohort analysis design by reviewing a record of RPGN patients who were on follow-up. The observation was made from January 1st, 2016 to January 31st, 2023.

4.3. Source and Study Population

The source population was all patients with clinically diagnosed RPGN who had been on follow-up at the hospital during the observation period.

The study population was all eligible patients with clinically diagnosed RPGN who had been on follow-up at the hospital during the observation period.

4.4. Eligibility Criteria

4.4.1. Inclusion criteria

All adult patients who were clinically diagnosed with RPGN at the hospital during the observation period and received immunosuppressive therapy for at least 1 month were included in the study.

4.4.2. Exclusion Criteria

- Patients who were later diagnosed to have an alternative diagnosis than RPGN
- Patients with missing information on the outcome or major exposure variables on their medical records and for which secondary data source to identify the missing information cannot be obtained

4.5.Sample size and sampling technique

Due to the small size of the source population, the sample size was not calculated. Based on the eligibility criteria, 45 eligible patients were identified and all were included in the study.

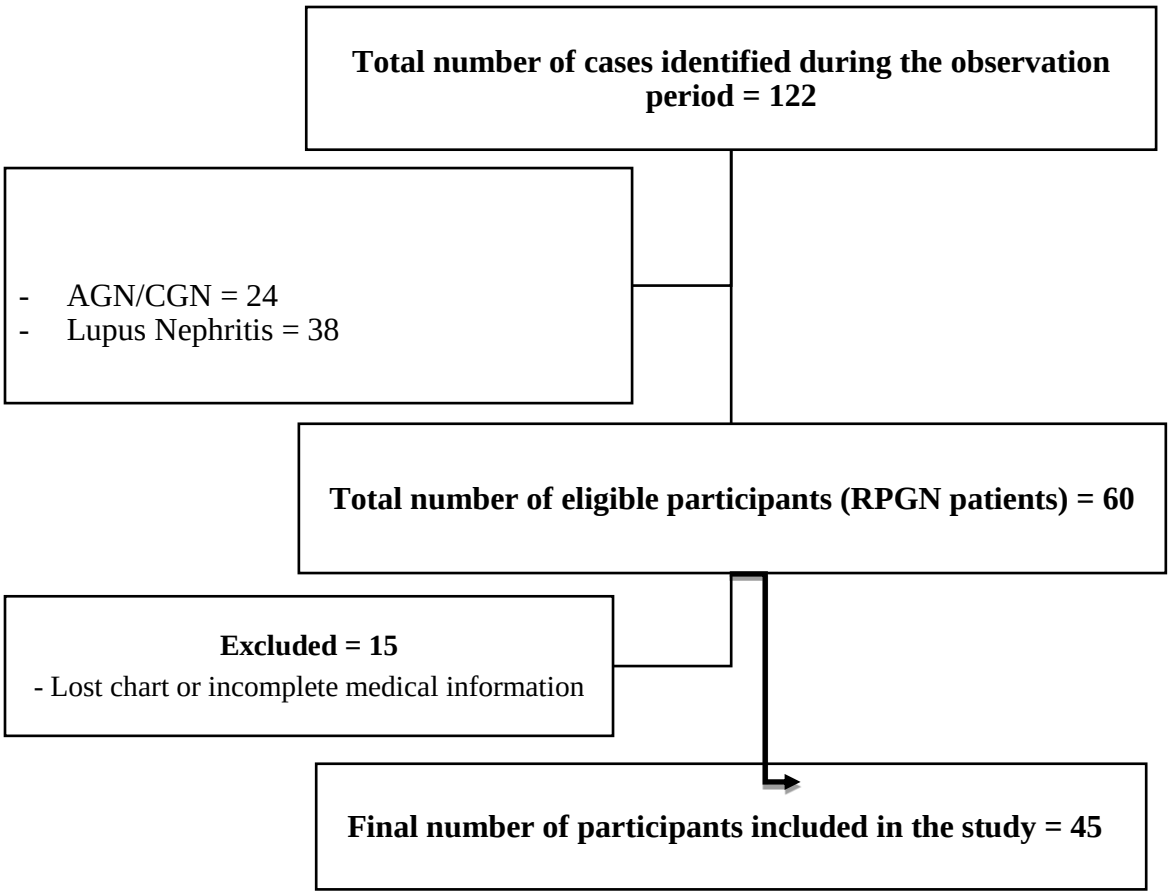

Figure 2: Flow chart showing the recruitment of eligible study participants in the research

4.6.Study variables

4.6.1. Outcome variable

- Treatment outcome (Complete remission, Partial remission, CKD, ESRD, Death)

4.6.2. Exposure variables

- **Socio-demographic characteristics**
  - Age, sex, place of residence
- **Comorbidities**
  - Diabetes mellitus, CVD [HF, IHD, Stroke], HIV, others
- **Clinical Profile, Baseline Characteristics and Investigations**
  - Baseline clinical profile
  - Duration of illness
  - Renal symptoms
  - Extra-renal symptoms

- Dialysis requirement
- Etiologic Immunologic Diagnostic Studies
- Etiologic Pathologic Diagnostic Studies

- **Clinical Diagnosis**
  - Clinical diagnosis of RPGN
  - Echo
  - Abdominal US
- **Treatment History**
  - Pulse Methylprednisolone
  - High Dose Corticosteroids
  - IV Cyclophosphamide
- **Treatment Response and adverse effects**
  - Serum Creatinine changes after starting treatment
  - Renal Treatment Response at 12 weeks and 24 weeks
  - Overall Patient Outcome
  - Complications (infectious, hematologic, and others)

4.7.Operational definitions

- **Clinical rapidly progressing glomerulonephritis:** nephritic syndrome or predominately nephritic syndrome and progressively declining GFR with normal or increased kidney sizes on ultrasonography with no evidence of active or recent infections.

- **End-stage kidney disease**: the requirement of renal replacement therapy for 12 consecutive weeks or more or a receipt of renal transplantation.

- **Complete remission:** Normalization of serum creatinine (eGFR>60ml/min) and 24-hour urine protein less than 500 mg; that occurred within 6 months from initiation of treatment.

- **Partial remission:** Decrement or stabilization of serum creatinine (eGFR 15-60ml/min) and reduction of proteinuria without a need for RRT 6 months from initiation of treatment.

- **Sustained remission:** A remission that occurred within six months and is sustained for at least 12 months from the initiation of treatment.

- **Treatment failure:** Increment in serum creatinine from baseline (GFR<60ml/min), stabilization of serum creatinine if GFR remains <15 ml/min, need to initiate or continue RRT after six months of initiation of therapy; irrespective of the duration of therapy received.

- **Death:** death from any cause that occurred after receiving at least two weeks of immunosuppressive therapy.

- **Lost to follow-up:** data related to outcomes cannot be obtained, but there is documentation that the patient has been prescribed immunosuppressive medications.

- **Serious Infection:** an infectious syndrome that requires intravenous antibiotics or hospitalization for treatment or causes death.

- **Relapse:** Documented worsening of disease activity (progressive increment in serum creatinine done at least one week apart with proteinuria and hematuria) after any period of remission.

- **CKD**: Abnormalities of kidney structure or function, present for >3 months, with health implications.

4.8.Data Collection procedures and quality assurance

Data was collected from the patient's medical record (charts, HMIS reports, and electronic databases) using a data abstraction tool that consists of all the above exposure and outcome variables. A pretest on 5% of randomly selected medical charts was made and the necessary revision to the data collection tool was made based on the test result.

The principal investigator gave training on the basics of the data abstraction form and on how to use the form appropriately for three senior internal medicine residents and one supervisor (nephrology fellow) for one day. The collected data was checked for its consistency and completeness before any attempt to enter code and analyze it.

4.9. Data management and analysis

Data was summarized using frequencies (percentages) and bar graph for categorical variables and numerical variables were summarized with a mean ± standard deviation (SD) or median with Interquartile range (IQR) values, as required after testing the assumption of normality using

Kolmogorov-Smirnov and Shapiro-wilk test where p-value of ≤0.05 indicated skewed distribution.

Creatinine level was recorded at baseline, treatment initiation, and during follow-up at 4 weeks, 8 weeks, 12 weeks, and 24 weeks. The change from the time of treatment initiation at each follow-up duration was measured as an absolute and percent change in mean creatinine value and the result was presented using an Error Bar graph.

Follow-up eGFR was presented using an Error Bar graph by using the mean with 95 CI of eGFR values collected at 1^{st} week, 3^{rd} month, 6^{th} month, 1^{st} year, 2^{nd} year, and 3^{rd} year of follow-up. Furthermore, follow-up graft function with the stage of CKD was presented using a Bar graph for all the same follow-up times.

Comparison of several infectious complications and patient outcomes were compared between groups classified by patients' socio-demographic and clinical characteristics to identify the presence of significant differences. Accordingly, for categorical variables, a comparison was done using the chi-square test after testing the assumption that no cell has an expected count of less than 5. For variables with failed assumptions, Fischer's exact test was used. For numeric variables, a test of normality was run first and it was found that age had a normal distribution and cumulative dose of cyclophosphamide had a skewed distribution. Hence, to compare age with infectious complication and patient outcome, independent t-test and one-way ANOVA were used respectively. Furthermore, to compare the cumulative dose of cyclophosphamide with infectious complications and patient outcome, the Mann-Whitney U-test and Kruskal Wallis test were used respectively.

4.10 Ethical considerations

The study will be conducted after obtaining ethical clearance from the Department of Internal Medicine Research and Ethics Committee and IRB of the College of Health Sciences, Addis Ababa University. Since it is a retrospective record review study, the research and Ethics committee will waive consent. Medical record numbers will be used for the data collection and personal identifiers of the patient will not be used in the research report. Access to the collected information will be limited to the principal investigator and confidentiality will be maintained throughout the project.

5. RESULTS

5.1. Sociodemographic and Presenting Clinical Characteristics

The median age of the participants was 37 years (IQR, 25.0-51.5 years) ranging from 13 to 73 years. In addition, of the 45 patients, four were under the age of 18 years. Over half (25/45) were females and resided in Addis Ababa (21/45) or Oromia region (15/45). The most common comorbid illnesses were hypertension (13/45), HIV (4/45), and Asthma(3/45). Thirteen patients (13/45) were taking anti-hypertensive medication.

The median duration of illness was 14.0 days (IQR, 9.5-28.0 days). A history of Oliguria was documented in 35/45 patients. Nearly half of the patients experienced one or more extra-renal symptoms, with the majority presenting with respiratory complaints (22/45), pulmonary manifestations (13/45), upper respiratory tract symptoms (9/45), and rheumatologic manifestations (9/45). Upon presentation, the average systolic and diastolic blood pressures were 139.6 ± 24.3 mmHg and 81.9 ± 15.9 mmHg, respectively. Twelve out of 45 patients required dialysis during the disease. **(Table 1)**

Table 1: Socio-demographic and presenting clinical characteristics of clinically diagnosed RPGN patients who were on follow-up at Tikur Anbessa Specialized Hospital in Ethiopia from January 1st, 2016 to January 31st, 2023 (n=45).

Variable	Frequency	Variable	Frequency
Age in years (Median, IQR)	37.0 (25.0-51.5)	Scleroderma	1
Sex		Colonic diverticulitis	1
Male	20	Late Pregnancy	1
Female	25	**Medication**	
Place of residence		Anti-hypertensive	13
Addis Ababa	21	**Duration of illness in days** (Median, IQR)	14.0 (9.5-28.0)
Oromia	15	**History of Oliguria**	
Amhara	7	No	10
SNNPR	2	Yes	35

Comorbidities		**Extra-renal symptoms**	
Hypertension	13	Respiratory	22
HIV	4	Pulmonary	13
URT/Asthma Sx	3	Upper respiratory	9
Diabetes Mellitus	1	Rheumatological (Joints/Skin)	9
Health Failure	1	CNS	3
CLD	1	**SBP in mmHg** (Mean ± SD)	139.6 ± 24.3
DVT	1	**DBP in mmHg** (Mean ± SD)	81.9 ± 15.9
Dyslipidemia	1	**Dialysis requirement**	
Latent Syphilis	1	No	33
		Yes	12

5.2.Laboratory biomarkers and radiologic features

Laboratory biomarkers were available for less than half of the patients. Among those tested, low levels of C3, C4, and Anti-dsDNA were documented in 9/22, 3/20, and 2/10 patients, respectively. Additionally, ANA was positive in 5/22 patients, and ANCA was positive in 2/11 patients (one P-ANCA and one C-ANCA type). Almost all patients (44/45) had active urinary sediments, and 24-hour urine protein was 1 gram or higher. The remaining patient was anuric. The median change in serum creatinine from baseline to treatment initiation was 3.9 mg/dl (IQR, 1.95-9.83 mg/dl).

Renal biopsy was performed on only four patients. The results were 2 MPGN, C3GN, and C3GN rule out PSGN. Echocardiography results were documented for only 14 patients, of whom 11 had abnormal findings, including left ventricular hypertrophy (LVH) in 5/11 patients, dilated cardiomyopathy (DCMP) in 2/11 patients, and mild pericardial effusion in 2/11 patients. Abdominal ultrasound results were documented for 40/45 patients, and the results showed that all had normal-sized kidneys. The most common abnormal findings were bilateral echogenic and enlarged kidneys (3/12 patients), bilateral parenchymal disease (2/12 patients), and bilateral echogenic kidneys with poor Corticomedullary differentiation (2/12 patients). **(Table 2)**

Table 2: Laboratory biomarkers and radiologic features of clinically diagnosed RPGN patients who were on follow-up at Tikur Anbessa Specialized Hospital in Ethiopia from January 1st, 2016 to January 31st, 2023 (n=45).

Variable	Frequency	Variable	Frequency
C3 level (n=22)		**Renal Biopsy Done**	
Low	9	No	41
Normal	13	Yes	4
C4 level (n=20)		**Echocardiography (n=14)**	
Low	3	Normal	3
Normal	17	LVH	5
Anti-dsDNA (n=10)		DCMP	2
Low	2	Mild pericardial effusion	2
Normal	9	Bilateral pleural effusion	1
ANA Qualitative (n=22)		Moderate pulmonary hypertension	1
Negative	17	Hyperdynamic Heart	1
Positive	5	**Abdominal US**	
ANCA (n=11)		Normal	28
Negative	9	Bilateral echogenic Kidney and enlarged	3
Positive	2	Bilateral parenchymal disease with poor CM diff	4
Anti-GBM (n=2)			
Negative	2	Bilateral echogenic kidney with exaggerated CM diff	1
Positive	0	Fatty liver and ascites	2
Active Urinary Sediments and 24-hour protein ≥ 1gm		Echogenic Right kidney and non-visualized left kidney	1
No; Anuric	1	Shrunk right kidney	1
Yes	44	Trabeculated Bladder/cystitis	1
Change in Serum Creatinine in mg/dl (Median, IQR)	3.90 (1.95, 9.83)		

5.3.Treatment history, response and complications

Pulse methylprednisolone was administered to 37/45 patients, with most receiving a dose of 500 mg (30/37 patients). High-dose corticosteroids were administered to 42/45 patients, including the remaining eight patients who did not take pulse methylprednisolone. Thirty-four patients (34/45) patients took both pulse methylprednisolone and high-dose corticosteroids. Furthermore, intravenous cyclophosphamide was administered to all patients but details were available for 36/45 patients; it was primarily administered every month (29/36 patients). The median number of cyclophosphamide doses administered was 3.0 (IQR, 1-6 doses), and the median cumulative dose received was 1500 mg (minimum dose of 500 mg and maximum dose of 7000 mg). Thirty (30/45) patients took all three regimens.

Renal treatment response was documented at 12 and 24 weeks for 22 and 23 patients, respectively. Data for the remaining patients was unavailable due to loss to follow-up or death before these time points. Among the documented cases, 20 patients exhibited a significant decrease in Cr in the 12th week. At the subsequent 24-week follow-up, 19 patients maintained this significant decrease, while one patient required dialysis. For one patient, data was only available in the 24th week, and the patient had a significant decrease in Cr at that time point. Three patients experienced stabilization of Cr levels at both time points, while the remaining two patients showed a progressive increase in Cr levels at both time points.

Following treatment, infectious complications were developed in 15/45 patients, 13 cases occurred within the first 12 weeks of follow-up and two cases occurred at 24 weeks. The most frequent complication was hospital-acquired infection (HAP) (4/15), tuberculosis (TB) (4/15), and gastrointestinal infection (4/15) followed by herpes zoster (3/15), genitourinary infection (1/15), and pericardial effusion with tamponade (1/15). Additionally, hematologic complications and steroid-induced diabetes mellitus were documented in 4/45 and 2/45 patients, respectively. Furthermore, 9/45 patients required hospitalization due to adverse effects of treatment. **(Table 3)**

Table 3: Treatment history and the response of clinically diagnosed RPGN patients who were on follow-up at Tikur Anbessa Specialized Hospital in Ethiopia from January 1st, 2016 to January 31st, 2023 (n=45).

Variable	Frequency	Variable	Frequency
Pulse Methylprednisolone		**Cumulative Cyclophosphamide dose received** (Median, IQR)	4800 (1312-6000)
No	8	**Renal Response at 12 weeks**	
Yes	37	Significant Decrement in Cr [Baseline >25%] and Off Dialysis	20
Dose of Methylprednisolone		Stabilization of Cr [Baseline ± 25%] and Off Dialysis	3
500 mg	30	Increment of Cr [Baseline >25%] or New HD Requirement or Remained on HD	2
1000 mg	6	**Renal Response at 24 weeks**	
750mg	1	Significant Decrement in Cr [Baseline >25%] and Off Dialysis	20
High Dose Corticosteroids		Stabilization of Cr [Baseline ± 25%] and Off Dialysis	3
No	3	Increment of Cr [Baseline >25%] or New HD Requirement or Remained on HD	3
Yes	42	**Adverse effects of treatment**	
IV Cyclophosphamide		Infectious Complications in 12 weeks	13
No	0	Infectious Complications in 24 weeks	2
Yes	45	Hospitalization	9
Frequency of		Hematologic complications	4

Cyclophosphamide administration			
Q2Weeks	2	Steroid-induced diabetes mellitus	2
Q4Weeks	29	Pulmonary thromboembolism	1
Cyclophosphamide doses administered (Median, IQR)	5.0 (2-6)	Angioedema	1
		Hemorrhagic cystitis	1

Follow-up Cr was documented for 35/45 patients in the 4th week, 25/45 patients in the 8th week, 23/45 patients in the 12th week, and 22/45 patients in the 24th week. The mean absolute change in Cr showed a progressive increase during the follow-up periods of 4 weeks, 8 weeks, and 12 weeks, with values of 3.8 ± 3.2 mg/dL, 4.0 ± 3.3 mg/dL, and 5.2 ± 3.9 mg/dL, respectively. Similarly, the mean percent change in Cr also increased during these follow-up periods, with values of 50.8 ± 22.5%, 64.9 ± 24.5%, and 67.8 ± 24.5%. In contrast, on the 24th week, there was a modest decline in the change in Cr from baseline compared to the change in the 12th week, with a mean absolute change in Cr of 4.5 ± 3.5 mg/dL and a mean percent change in Cr of 68.3 ± 29.5%. This pattern is also evident in the error bar below. **(Figure 3)**

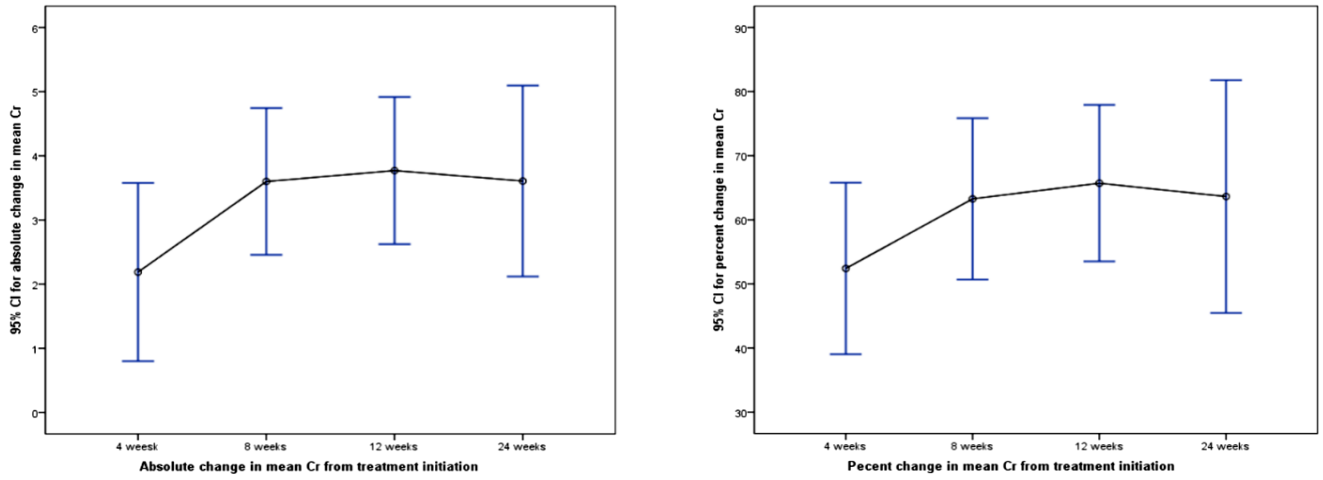

Figure 3: Absolute and percentage change in mean Cr at different times from treatment initiation among clinically diagnosed RPGN patients who were on follow-up at Tikur Anbessa Specialized Hospital in Ethiopia from January 1st, 2016 to January 31st, 2023.

5.4.Treatment outcome

From the 45 patients, complete follow-up was made for 34 patients and the remaining 11 patients were lost to follow-up. From the 34 who were followed at the hospital, 12 achieved complete recovery, 8 achieved partial remission, and 6 cases progressed. Of those who progressed, 4 developed CKD, and 2 progressed to ESRD. The rest 8 patients died. **(Figure 4)**

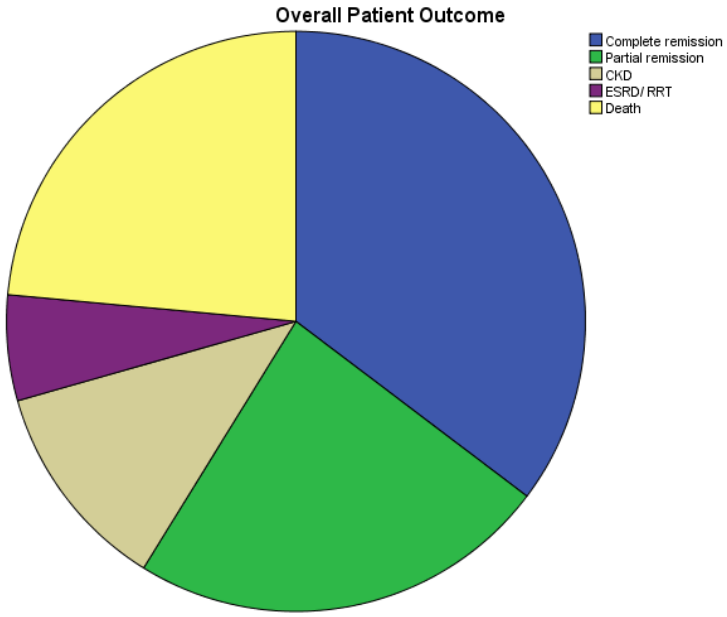

Figure 4: Patient outcome following treatment among clinically diagnosed RPGN patients who were on follow-up at Tikur Anbessa Specialized Hospital in Ethiopia from January 1st, 2016 to January 31st, 2023

5.5.Comparison of treatment outcome between groups

The distribution of patient demographic and clinical characteristics in terms of treatment outcomes were compared and it showed that a significant difference was identified between some of the groups. Accordingly, a significantly higher proportion of infectious complications were documented among patients who had URT/Asthma Sx(3/3 vs. 12/42, p=0.032) and those who required dialysis (9/12 vs. 6/33, p<0.001).

Regarding patient outcome, a significantly higher proportion of death was documented among patients with HIV (2/4 vs. 6/30, p=0.030) and those who required hospitalization due to adverse effects of treatment (5/7 vs. 1/7, p=0.029). Furthermore, a significantly higher proportion of remission (partial or complete) was documented among patients who took pulse methylprednisolone in any dose (19/28 vs. 1/6, p=0.013) and those who took a larger cumulative dose of cyclophosphamide (4400 mg Vs 2500 mg Vs 9000 mg, p=0.032) **(Table 4).**

Table 4: Comparison of infectious complication and patient outcome based on underlying characteristics of clinically diagnosed RPGN patients who were on follow-up at Tikur Anbessa Specialized Hospital in Ethiopia from January 1st, 2016 to January 31st, 2023 (n=45).

Variable	Infectious Complications		p-value	Patient outcome			p-value
	No	Yes		Complete/Partial remission	CKD/ ESRD	Death	
Age (In years**)** **(**Mean ± SD**)**	38.9 ± 13.8	36.1 ± 18.0	0.561	39.7 ± 14.9	41.8 ± 22.3	40.4 ± 16.5	0.963
Sex							
Male	13	7	0.832	8	3	4	0.899
Female	17	8		12	3	4	
HIV							
No	28	13	0.591	20	4	6	**0.030 ***
Yes	2	2		0	2	2	
Hypertension							
No	21	11	0.999	11	5	7	0.261

Yes	9	4		9	1	1	
Asthma							
No	30	12	**0.032***	17	6	8	0.746
Yes	0	3		3	0	0	
Dialysis Requirement							
No	27	6	**<0.0001***	16	4	4	0.256
Yes	3	9		4	2	4	
Pulse Methylprednisolone							
No	5	3	0.999	1	1	4	**0.013***
Yes	25	12		19	5	4	
Dose of Methylprednisolone							
500 mg	22	8	0.360	17	4	4	**0.044***
1000 mg	3	3		2	1	0	
750mg	0	1		0	0	0	
High Dose Corticosteroids							
No	3	0	0.540	1	0	0	0.999
Yes	27	15		19	6	8	
Cumulative dose of cyclophosphamide (in mg) (Median with IQR**)**	1375 (500-4800)	2900 (500-6000)	0.381	4400 (1125-5850)	2500 (875-6000)	900 (500-1438)	**0.032***
Hospitalization requirement							
No	2	6	0.206	6	0	1	**0.029***
Yes	0	9		1	1	5	

5.6 Predictors of patient's outcome

Multinational regression was conducted after linearity and multicollinearity assumption was assured. The outcome variables were categorized into three groups remission (complete remission and partial remission), no remission (ESRD, CKD), and death. Based on this only infection complications were found as statistically significant variables both with no remission and death. Patients who had infection were about 2.3 times more likely to develop no remission and 5.01 times more likely to die. Despite not reaching a significant level most of the variables were found as risk factors. For example, patients with male sex, oliguria at presentation, and hypertensive are about 3.67, 4.51, and 2.34 more likely to die **(Table 5).**

Table 5: Multinomial regression of predictors outcome among clinically suspected RPGN patients

Variables	**No remission AOR (95 %CI)**	**P value**	**Death AOR (95%CI)**	**P value**
Male	1.34(0.60,1.58)	0.34	3.69(0.72,18.76)	0.14
Age range(years)	1.01(0.97,1.05)	0.62	1.04(0.98,1.09)	0.18
Duration (Week)	1.04(0.90,1.19)	0.611	1.06(0.86,1.30)	0.57
Oliguria at presentation	1.77(0.66,4.77)	0.26	4.51(0.71,28.68)	0.11
Hypertension	1.97(0.72,5.38)	0.18	2.34(0.52,10.51)	0.26
Extrarenal manifestation	1.95(0.61,6.22)	0.27	1.06(0.86,1.30)	0.57
Cyclophosphamide	0.74 (0.35,3.42)	0.87	0.86(0.20,6.59)	0.86
Infection complication	2.31(0.78,6.82)	0.13	5.01(1.16,21.57)	**.031**

6. DISCUSSION

The study assessed the clinical profile and outcome of clinically diagnosed RPGN patients who were on follow-up at Tikur Anbessa Specialized Hospital in Ethiopia from January 1st, 2016 to January 31st, 2023. During the seven-year observation period, only 45 RPGN patients who fulfilled the inclusion criteria were included in the study. The median age of the patients was 37 years (ranging from 13 to 73 years). In addition, of the 45 patients, four were under the age of 18 years. The age pattern is by previous studies where one of the peak average ages for RPGN diagnosis is 30 years [17, 18]. It is also reported that RPGN is a disease of the young in the African population with a mean age of 30.7 to 33.9 years. Furthermore, several pediatric cases are also reported from Africa although RPGN is reported to be very rare in the developed countries [26-29].

In this study, a comparable sex distribution was seen, where 25/45 were females and 20/45 were males. This lack of gender-based disparity is also evident from other literature so far including large-scale systematic review and meta-analysis studies in Africa [26-29]. The most common comorbid illness identified in this study was hypertension (13/45 patients). This number is lower than previous studies where up to half of RPGN patients were reported to present with hypertension [13, 17, 25].

The median duration of illness was 14.0 days (IQR, 9.5-28.0 days). This implies that most of the patients experienced an abrupt onset. In such cases, symptom duration as low as one week is also reported. However, in cases with insidious onset type, symptom duration can be as long as two years [21, 25]. The most common presenting symptoms in this study were oliguria (35/45 patients) and extra-renal manifestations, mainly respiratory (22/45 patients), pulmonary (13/45 patients), upper respiratory tract (9/45 patients), and rheumatologic (9/45 patients). This finding is in line with other studies where the most frequently reported symptoms are renal symptoms including and mainly oliguria [19-22]. Similarly, studies from Africa also revealed that oliguria is among the top frequent presenting symptoms in these patients [26, 28-29]. Additionally, although it is reported that symptom presentation, including the extra renal manifestation, differs depending on the type of RPGN and other personal factors, the most frequently reported extra-

renal manifestations arise from the lung, followed by the nose/sinuses, joints, muscle, skin, and the nervous system [21, 22].

Laboratory biomarkers were available for less than half of the patients. Among those tested, low levels of C3, C4, and Anti-dsDNA were documented in 9/22, 3/20, and 2/10 patients, respectively. Additionally, ANA was positive in 5/22 patients, and ANCA was positive in 2/11 patients (one P-ANCA and one C-ANCA type).

Pulse methylprednisolone was administered to 37/45 patients, with most receiving a dose of 500 mg (30/37 patients). High-dose corticosteroids were administered to 40/45 patients. Furthermore, intravenous cyclophosphamide was administered to 36/45 patients, primarily every month (29/36 patients). The median number of cyclophosphamide doses administered was 5.0 (IQR, 2-6 doses), and the median cumulative dose received was 4800 mg (IQR, 1312-6000 mg).

Following treatment, the most common complication was infectious complications which were developed in 15/45 patients, followed by hematologic complications which were documented in 4/45 patients. Infection was also reported to be a common secondary complication in up to 67.0% of patients in a study conducted in India. In a similar study, however, anemia was diagnosed in 90.0% of patients, showing that it is the most common complication [38].

Renal treatment response was documented at 12 and 24 weeks for 22 and 23 patients, respectively. The majority (20 patients) showed a significant decrease in Cr, three patients experienced stabilization of Cr levels, and the remaining two patients showed a progressive increase in Cr levels. Furthermore, from the 45 patients, complete follow-up was made for 34 patients and the remaining 11 patients were lost to follow-up. From the 34 who were followed at the hospital, 12 achieved complete recovery, eight achieved partial remission, and six cases progressed. Of those who progressed, four developed CKD, and two progressed to ESRD. The rest eight patients died. The rate of complete or partial remission of 58.8% is higher than in other studies where only up to one-fifth of patients showed remission and the remaining progress to chronic kidney disease despite comprehensive management [24-25, 38-40]. This brings up the question of whether are we treating our clinically suspected RPGN patients who may have had a benign disease, to begin with. This is also evident from a report in Africa where a recovery rate of only 18.2% was achieved [28].

Furthermore, a significantly higher proportion of infectious complications were documented among patients who had URT/Asthma Sx and those who required dialysis. This has been demonstrated in several studies where pulmonary renal syndrome patients develop infections with immunosuppression [19-22]. Those who require dialysis also are predisposed to infections because of the severity of the renal injury and hospitalization, making them more prone to infections and access-related infections that might have occurred during their stay.

Regarding patient outcome, a significantly higher proportion of deaths was documented among patients with HIV and those who required hospitalization due to adverse effects of treatment. These patients are more prone to worsening infections while on immunosuppression. Those who are hospitalized have severe infections and more deaths than those seen for infections as an outpatient.

Furthermore, a significantly higher proportion of remission (partial or complete) was documented among patients who took pulse methylprednisolone in any dose (and those who took a larger cumulative dose of cyclophosphamide. This has been demonstrated in several studies that the more aggressive the immunosuppression the better the response at the earlier stages of RPGN, but at the cost of risking more infections as well.

7. STRENGTHS AND LIMITATIONS

The study has the following limitations: First, the study is a retrospective single-center study and the sample size was small. Second, the study is based on a hospital registry, and several key data required for analysis, that may affect the patient's outcome were absent. Third, due to the small sample size further analysis to identify significant predictors of outcome and survival time was not done.

However, the study has strengths: one, this is the first study conducted to assess the magnitude of clinically suspected RPGN patients in Ethiopia over a prolonged study period. Second, we tried to show the complete picture of the clinically suspected cases of RPGN including the clinical characteristics, the period of presentation, and treatment outcomes. Finally, in this study, clinically suspected RPGN patients were included, whereas most studies only included biopsy-proven RPGN patients; this could help in developing countries without histopathologic services and address their challenges in management through experience sharing.

8. CONCLUSION

In this study, we found that the patients presented late with a varied clinical picture, the majority were hypertensive and required dialysis at the initial visit. Nearly half of the patients experienced one or more extra-renal symptoms, with the majority presenting with respiratory complaints. Renal biopsy was done for only four patients from forty-five patients.

Most of the patients had a significant decrease in Cr at the 12th week and at the subsequent 24-week follow-up. A significantly higher proportion of remission (partial or complete) was documented among patients who took a larger cumulative dose of cyclophosphamide. Following treatment, infectious complications developed in 15 patients, from the 45 patients.

Of the 45 patients, 20 patients had complete or partial remission and six cases progressed. Of those who progressed, four developed CKD, and two progressed to ESRD. The rest 8 patients died. The rate of complete or partial remission is much higher than in other studies.

9. RECOMMENDATION

First, since clinically suspected RPGN patients in this study had little histologic diagnosis; we recommend strengthening the renal pathology service to have an early histologic diagnosis and initiation of timely immunosuppressive treatment for those with Crescentric RPGN and de-escalating immunosuppression for those with benign diseases.

Second, in certain severely ill patients, renal biopsy cannot always be smoothly and quickly performed, so serologic tests that are important for the diagnosis and follow-up of RPGN patients should be available in the country. Specific high-quality Ag-specific markers [serum immunoassays myeloperoxidase (MPO-ANCA) or proteinase 3 (PR3-ANCA)] are important and are more correlated with AAV than immunofluorescence C/P ANCA.

Third, Early referral to specialized centers with dedicated nephrology services should be practiced for such groups of patients, to give proper immunosuppression before the disease becomes more advanced and progresses to ESRD requiring hemodialysis.

Fourth, infection prevention measures should be increased in these particularly vulnerable patients on a prolonged course of immunosuppression, weighing the risks and benefits of therapy.

Finally, further prospective multi-center research studies with larger sample sizes should be done for further analysis to identify significant predictors of outcome and survival of RPGN patients, to improve the clinical management of these patients.

REFERENCES

1. Parmar MS, Bashir K. Crescentic Glomerulonephritis. [Updated 2023 Feb 20]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-.
2. Davies DJ, Moran JE, Niall JF, et al. Segmental necrotizing glomerulonephritis with antineutrophil antibody: possible arbovirus etiology? Br Med J (Clin Res Ed). 1982 Aug 28-Sep 4. 285(6342):606.
3. Lingaraj U, Mallappa SS, Neminah RE, Mohan SM, Venkatesh L, Gurusiddaiah SC, et al. A "Mini-Epidemic" of anti-glomerular basement membrane disease: Clinical and epidemiological study. Saudi J Kidney Dis Transpl. 2017 Sep-Oct. 28 (5):1057-1063.
4. Kawai H, Banno S, Kikuchi S, Nishimura N, Nobata H, Kimura Y, et al. Retrospective analysis of factors predicting end-stage renal failure or death in patients with microscopic polyangiitis with mainly renal involvement. ClinExpNephrol. 2014 Oct. 18(5):795-802.
5. Andrassy K, Kuster S, Waldherr R, et al. Rapidly progressive glomerulonephritis: analysis of prevalence and clinical course. Nephron. 1991. 59(2):206-12.
6. Bacani RA, Velasquez F, Kanter A, et al. Rapidly progressive (nonstreptococcal) glomerulonephritis. Ann Intern Med. 1968 Sep. 69(3):463-85.
7. Couser WG. Rapidly progressive glomerulonephritis: classification, pathogenetic mechanisms, and therapy. Am J Kidney Dis. 1988 Jun. 11(6):449-64.
8. Moroni G, Ponticelli C. Rapidly progressive crescentic
9. Stilmant MM, Bolton WK, Sturgill BC, et al. Crescentic glomerulonephritis without immune deposits: clinicopathologic features. Kidney Int. 1979 Feb. 15(2):184-95.
10. Glomerulonephritis: Early treatment is a must. Autoimmun Rev. 2014 Jul. 13(7):723-9.
11. Jones RB, Cohen Tervaert JW, Hauser T: Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med 363:211-220, 2010. doi: 10.1056/NEJMoa0909169
12. Walsh M, Merkel PA, Peh C-A, et al: Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. N Engl J Med 382(7):621-631, 2020. doi: 10.1056/NEJMoa1803537
13. Levy JB, Turner AN, Rees AJ, et al: Long-term outcome of anti-glomerular basement membrane antibody disease treated with plasma exchange and immunosuppression. Ann Intern Med 134(11):1033-1042, 2001. doi: 10.7326/0003-4819-134-11-200106050-00009

14. Aydin Z, Turkmen K, Dede F, et al, Demographic, clinical and laboratory characteristics of rapidly progressive glomerulonephritis in Turkey: Turkish Society of Nephrology-Glomerular Diseases (TSN-GOLD) Working Group. ClinExpNephrol. 2021 Feb;25(2):173-183. doi: 10.1007/s10157-020-01978-6. Epub 2020 Oct 11. PMID: 33040246.
15. Berti A, Cornec-Le Gall E, Cornec D, Casal Moura M, Matteson EL, Crowson CS, Ravindran A, Sethi S, Fervenza FC, Specks U. Incidence, prevalence, mortality and chronic renal damage of anti-neutrophil cytoplasmic antibody-associated glomerulonephritis in a 20-year population-based cohort. Nephrol Dial Transplant. 2019 Sep 01;34(9):1508-1517.
16. Lingaraj U, Mallappa SS, Neminah RE, Mohan SM, Venkatesh L, Gurusiddaiah SC, Rachaiah NM. A "Mini-Epidemic" of anti-glomerular basement membrane disease: Clinical and epidemiological study. Saudi J Kidney Dis Transpl. 2017 Sep-Oct;28(5):1057-1063. doi: 10.4103/1319-2442.215128. PMID: 28937063.
17. Moutzouris DA, Herlitz L, Appel GB, Markowitz GS, Freudenthal B, Radhakrishnan J, D'Agati VD. Renal biopsy in the very elderly. Clin J Am SocNephrol. 2009 Jun;4(6):1073-82.
18. Lingaraj U, Mallappa SS, Neminah RE, Mohan SM, Venkatesh L, Gurusiddaiah SC, Rachaiah NM. A "Mini-Epidemic" of anti-glomerular basement membrane disease: Clinical and epidemiological study. Saudi J Kidney Dis Transpl. 2017 Sep-Oct;28(5):1057-1063.
19. Takahashi-Kobayashi M, Usui J, Kaneko S, Sugiyama H, Nitta K, Wada T, et al. (2020) Age-dependent survival in rapidly progressive glomerulonephritis: A nationwide questionnaire survey from children to the elderly. PLoS ONE 15 (7): e0236017. https://doi.org/10.1371/journal. pone.0236017
20. Kantauskaitė M, Laučytė-Cibulskienė A, Miglinas M. Histopathological Classification-A Prognostic Tool for Rapidly Progressive Glomerulonephritis. Medicina (Kaunas). 2018 Apr 17;54(2):17. doi: 10.3390/medicina54020017. PMID: 30344248; PMCID: PMC6037248.
21. Cassidy MJ, Gaskin G, Savill J, Pusey CD, Rees AJ. Towards a more rapid diagnosis of rapidly progressive glomerulonephritis. BMJ. 1990 Aug 11;301(6747):329-31. doi: 10.1136/bmj.301.6747.329. PMID: 1975508; PMCID: PMC1663619.

22. Alchi B, Griffiths M, Sivalingam M, Jayne D, Farrington K. Predictors of renal and patient outcomes in anti-GBM disease: clinicopathologic analysis of a two-centre cohort. Nephrol Dial Transplant. 2015 May;30(5):814-21.
23. Chan CE, Ng TJ, Ahmad MK, Mohamad Nor FS. Antineutrophil Cytoplasmic Autoantibody-Negative Pauci-Immune Crescentic Glomerulonephritis in a Patient with Systemic Lupus Erythematosus. Case Rep Nephrol Dial. 2022 Oct 20;12(3):201-206. doi: 10.1159/000527248. PMID: 36465575; PMCID: PMC9710425.
24. Han, Fei, Chen, Liangliang MD, Le, Jingyun MD, et al, The Clinicopathologic Spectrum of Rapidly Progressive Glomerulonephritis Based on Glomerular Immune Deposition and Antineutrophil Cytoplasmic Antibody. Applied Immunohistochemistry & Molecular Morphology 23(10):p 704-710, November/December 2015. | DOI: 10.1097/PAI.0000000000000134
25. Hedger N, Stevens J, Drey N, Walker S, Roderick P. Incidence and outcome of pauci-immune rapidly progressive glomerulonephritis in Wessex, UK: a 10-year retrospective study. Nephrol Dial Transplant. 2000 Oct;15(10):1593-9. doi: 10.1093/ndt/15.10.1593. PMID: 11007827.
26. MEEL, S, POS-155 A FIVE YEAR RETROSPECTIVE STUDY TO DETERMINE THE CHARACTERISTICS OF RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS FROM THREE TERTIARY HOSPITALS IN GAUTENG, SOUTH AFRICA, Kidney International Reports, 6 (4), 2021, https://doi.org/10.1016/j.ekir.2021.03.165
27. ChisamboMwaba et al. Rapidly progressive glomerulonephritis in two Zambian children: a case report. Pan African Medical Journal. 2022;42:21. [doi: 10.11604/pamj.2022.42.21.33318]
28. Faye M, Tall Lemrabott A, Fall K, MoustaphaCherif Dial M, MoustaphaCisse M, et al. Crescentic Glomerulonephritis in a Sub-Saharan Country: Clinical Presentation, Etiological and Evolutive Profile. Nephro-Urol Mon. 2017;9(6):e60365. https://doi.org/10.5812/numonthly.60365.
29. Mohammad SM, Jummai S, Mustapha L, Umar L, Ibrahim U. Rapidly progressive glomerulonephritis in a tertiary health facility in northeastern Nigeria: Challenges in diagnosis and management. J Egypt SocNephrol Transplant 2023;23:68-71, https://www.jesnt.eg.net/text.asp?2023/23/2/68/372068

30. McAdoo SP, Pusey CD. Anti-Glomerular Basement Membrane Disease. Clin J Am SocNephrol. 2017 Jul 07;12(7):1162-1172.
31. Arimura Y, Muso E, Fujimoto S, Hasegawa M, Kaname S, Usui J, Ihara T, Kobayashi M, Itabashi M, Kitagawa K, Hirahashi J, Kimura K, Matsuo S. Evidence-based clinical practice guidelines for rapidly progressive glomerulonephritis 2014. ClinExpNephrol. 2016 Jun;20(3):322-41.
32. McGregor JG, Hogan SL, Hu Y, Jennette CE, Falk RJ, Nachman PH. Glucocorticoids and relapse and infection rates in anti-neutrophil cytoplasmic antibody disease. Clin J Am SocNephrol. 2012 Feb;7(2):240-7.
33. Faurschou M, Westman K, Rasmussen N, de Groot K, Flossmann O, Höglund P, Jayne DR., European Vasculitis Study Group. Brief Report: long-term outcome of a randomized clinical trial comparing methotrexate to cyclophosphamide for remission induction in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum. 2012 Oct;64(10):3472-7.
34. Geetha D, Hruskova Z, Segelmark M, Hogan J, Morgan MD, Cavero T, Eriksson P, Seo P, Manno RL, Dale J, Harper L, Tesar V, Jayne DR. Rituximab for treatment of severe renal disease in ANCA associated vasculitis. J Nephrol. 2016 Apr;29(2):195-201.
35. Walsh M, Merkel PA, Peh CA, Szpirt W, Guillevin L, Pusey CD, De Zoysa J, Ives N, Clark WF, Quillen K, Winters JL, Wheatley K, Jayne D., PEXIVAS Investigators. Plasma exchange and glucocorticoid dosing in the treatment of anti-neutrophil cytoplasm antibody-associated vasculitis (PEXIVAS): protocol for a randomized controlled trial. Trials. 2013 Mar 14;14:73.
36. Li ZY, Gou SJ, Chen M, Zhao MH. Predictors for outcomes in patients with severe ANCA-associated glomerulonephritis who were dialysis-dependent at presentation: a study of 89 cases in a single Chinese center. Semin Arthritis Rheum. 2013 Apr;42(5):515-21. doi: 10.1016/j.semarthrit.2012.09.005. Epub 2013 Jan 16. PMID: 23332902.
37. Lin W, Chen M, Cui Z, Zhao MH. The immunopathological spectrum of crescentic glomerulonephritis: a survey of 106 patients in a single Chinese center. Nephron Clin Pract. 2010;116(1):c65-74. doi: 10.1159/000314665. Epub 2010 May 21. PMID: 20502041.
38. Areca Wangnoo1, Pankaj Banotra1, S K Bali2, Study of the Clinical Profile of Rapidly Progressive Glomerulonephritis, International Journal of Research and Review Vol.7; Issue:

4; 286-294, April 2020,

39. Rampelli SK, Rajesh NG, Srinivas BH, et al. Clinical spectrum and outcomes of crescentic glomerulonephritis: A single-center experience. Indian Journal of Nephrology. 2016 Jul-Aug;26(4):252-256. DOI: 10.4103/0971-4065.158574. PMID: 27512296; PMCID: PMC4964684.
40. Kapitsinou PP, Ioannidis JP, Boletis JN, Sotsiou F, Nakopoulou L, Daphnis E, Moutsopoulos HM. Clinicopathologic predictors of death and ESRD in patients with pauci-immune necrotizing glomerulonephritis. Am J Kidney Dis. 2003 Jan;41(1):29-37. doi: 10.1053/ajkd.2003.50013. PMID: 12500219.
41. Day, CJ, Howie, AJ, Nightingale, P, Shabir, S, Adu, D, Savage, C &Hewins, P 2010, 'Prediction of ESRD in Pauci-immune Necrotizing Glomerulonephritis: Quantitative Histomorphometric Assessment and Serum Creatinine.', American Journal of Kidney Diseases, vol. 55, no. 2, pp. 250-258. https://doi.org/10.1053/j.ajkd.2009.10.047
42. Chen S, Tang Z, Xiang H, Li X, Chen H, Zhang H, Hu W, Zeng C, Liu Z. Etiology and Outcome of Crescentic Glomerulonephritis From a Single Center in China: A 10-Year Review. Am J Kidney Dis. 2016 Mar;67(3):376-83. doi: 10.1053/j.ajkd.2015.07.034. Epub 2015 Sep 19. PMID: 26388283.
43. Kaneko S, Yamagata K, Usui J, Tsuboi N, Sugiyama H, Maruyama S, Narita I. Epidemiology and temporal changes in the prognosis of rapidly progressive glomerulonephritis in Japan: a nationwide 1989-2015 survey. ClinExpNephrol. 2022 Mar;26(3):234-246. doi: 10.1007/s10157-021-02148-y. Epub 2021 Oct 13. PMID: 34643841.
44. Salmela A, Törnroth T, Poussa T, Ekstrand A. Prognostic Factors for Survival and Relapse in ANCA-Associated Vasculitis with Renal Involvement: A Clinical Long-Term Follow-Up Study. Int J Nephrol. 2018;2018:6369814.
45. Cao Y, Schmitz JL, Yang J, Hogan SL, Bunch D, Hu Y, Jennette CE, Berg EA, Arnett FC, Jennette JC, Falk RJ, Preston GA. DRB1*15 allele is a risk factor for PR3-ANCA disease in African Americans. J Am SocNephrol. 2011 Jun;22(6):1161-7.
46. Biesenbach P, Kain R, Derfler K, Perkmann T, Soleiman A, Benharkou A, Druml W, Rees A, Säemann MD. Long-term outcome of anti-glomerular basement membrane antibody disease treated with immunoadsorption. PLoS One. 2014 Jul 31;9(7):e103568. doi:

10.1371/journal.pone.0103568. PMID: 25079220; PMCID: PMC4117516.

47. Sinha A, Puri K, Hari P, Dinda AK, Bagga A. Etiology and outcome of crescentic glomerulonephritis. Indian Pediatr. 2013 Mar;50(3):283-8. doi: 10.1007/s13312-013-0095-z. Epub 2012 Aug 5. PMID: 23024099.
48. Sharon L. Ford, Kevan R. Polkinghorne, Anthony Longano, et al, Histopathologic and Clinical Predictors of Kidney Outcomes in ANCA-Associated Vasculitis, ORIGINAL INVESTIGATION PATHOGENESIS AND TREATMENT OF KIDNEY DISEASE| VOLUME 63, ISSUE 2, P227-235, 2013, https://doi.org/10.1053/j.ajkd.2013.08.025

ANNEX

Annex 1: Data Abstraction tool

1. STUDY ID_____
2. MRN _____

Part I: Sociodemographic characteristics

1. Age (in complete years) _____
2. Sex
    - Male
    - Female
3. Telephone Number
4. Place of residence
    - Addis Ababa
    - Tigray
    - Afar
    - Amhara
    - Oromia
    - Somali
    - Harari
    - Benishangul-Gumuz
    - Gambella
    - Sidama
    - SNNPR

Part II: Documented Comorbidities and Clinical Profile Before Treatment Initiation

1. Comorbidities
    - Diabetes Mellitus
    - CVD [HF, IHD, Stroke]
    - HIV
    - Others

Part III: Clinical Profile, Baseline Characteristics and Investigations

1. Clinical profile
    - SBP at Presentation []
    - DBP at Presentation[]
    - Antihypertensive [YES NO]
    - BMI []
2. Duration of Illness as reported in the History
    - Weeks []
3. Oliguria
    - History [YES NO]
    - Documented UOP during Hospitalization []
      [On the first day of Hospitalization, ER/Wards]
    - Maximum Dose of Diuretics Received in a Day []
4. Extra-renal symptoms [YES NO]
    - Upper respiratory manifestations
    - Pulmonary manifestations
    - CNS manifestations
    - Rheumatological manifestations [Joints/Skin]
5. Dialysis Requirement [YES NO]
6. Etiologic Immunologic Diagnostic Studies
    - C3 Levels [Low/ Normal]
    - C4 Levels [Low/ Normal]
    - ANA Qualitative [+ve/-ve]
    - ANA Quantitative [Low/ Normal]
    - Other Serology
        - AntidsDna [Low/ Normal]
        - ANCA [Type] [+ve/-ve]
            - MPO/PR3
            - P-Anca/C-Anca
        - AntiGbm [+ve/-ve]
7. Etiologic Pathologic Diagnostic Studies
    - Renal Biopsy Done [YES NO]

- If Yes,
    - Total glomeruli
    - Global sclerotic glomeruli
    - Crescentic glomeruli ratio (percentage)
    - Cellular crescentic glomeruli number
    - Fibroceluular crescentic glomeruli number
    - Type of RPGN

Part IV: Clinical Diagnosis

1. Does the patient fulfill the inclusion criteria for Clinical RPGN

   [YES NO]

   a) Clinical DX of RPGN [YES NO]
   b) Active Urinary Sediments and 24 hr protein ≥ 1gm [YES NO]
   c) Normal Kidney Sizes
      a. Right Kidney []
      b. Left Kidney []
      c. Reported as Normal
   d) Progressively rising Serum Cr in 2 weeks [YES NO]
      a. Change in Serum Creatinine from "Baseline" to Time of Rx Initiation []
      b. Serum Creatinine changes before Rx Initiation []
2. Exclusions

   IRGN Considerations [PSGN, Infective endocarditis, Sepsis, abscess, others..]

   a. HBsAg [+ve/-ve/NA]
   b. HCVAB [+ve/-ve/NA]
   c. VDRL [+ve/-ve/NA]
   d. ASO Titre [+ve/-ve/NA]
   e. Echocardiography
   f. Abdominal US

Part V: Treatment History

1. Pulse Methylprednisolone [YES NO UK]
2. Dose of Methylprednisolone [500 mg 1000 mg]
3. High Dose Corticosteroids [YES NO]
4. IV Cyclophosphamide [YES NO]
5. Frequency of Cyclophosphamide Administration [Q2Weeks Q4Weeks]
6. Number of Cyclophosphamide doses administered []
7. Cumulative Cyclophosphamide dose received []

Part VI: Treatment Response and Adverse Effects

1. **Serum Creatinine changes after starting treatment**
    a. 4 weeks [1 month]
        i. Absolute Change [4wks Cr – Cr at Rx Initiation]
        ii. Changes in Percentage
            [Cr at 4 wks – Cr at initiation]/ Cr at Initiation *100
    b. 8 weeks [2 month]
        i. Absolute Change [4wks Cr – Cr at Rx Initiation]
        ii. Changes in Percentage
            [Cr at 4 wks – Cr at initiation]/ Cr at Initiation *100
    c. 12 weeks [3 month]
        i. Absolute Change [4wks Cr – Cr at Rx Initiation]
        ii. Changes in Percentage
            [Cr at 4 wks – Cr at initiation]/ Cr at Initiation *100
    d. 24 weeks [6 month]
        i. Absolute Change [4wks Cr – Cr at Rx Initiation]
        ii. Changes in Percentage
            [Cr at 4 wks – Cr at initiation]/ Cr at Initiation *100

2. **Renal Treatment Response at 12 weeks and 24 weeks**
    a. Serum Cr and HD requirement
        i. Significant Decrement in Cr [Baseline >25%] and Off Dialysis
        ii. Stabilization of Cr [Baseline ± 25%] and Off Dialysis
        iii. Increment of Cr [Baseline >25%] or New HD Requirement or Remained on HD
3. **Overall Patient Outcome**
        i. Complete remission
        ii. Partial remission
        iii. CKD
        iv. ESRD/ RRT
        v. Death
        vi. Unknown
    a. DD/MM/YY remission achieved _____
    b. DD/MM/YY CKD diagnosed _____
    c. DD/MM/YY ESRD diagnosed _____
    d. DD/MM/YY patient died _____
4. **Adverse effects of Treatment**
    a. Infectious Complications Documented
        i. In 12 weeks [Yes No]
        ii. In 24 Weeks [Yes No]
        iii. If Yes
            1. Number of Infections []
            2. Type of Infections []
            3. Hospitalization requirement [Yes No]
    b. Hematologic Complications
        i. Leukopenia [Nadir WBC during Induction Period/06 months]
    c. Other Complications