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Outcomes of Rapidly Progressive Glomerulonephritis in children

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Abstract

Background: Rapidly Progressive Glomerulonephritis (RPGN) is a form of glomerulonephritis characterized by an acute nephritic illness. The outcome is determined by the severity of renal failure at presentation, promptness of intervention, and the underlying renal pathology.

Objectives: This study aimed to analyze the outcomes of pediatric rapidly progressive glomerulonephritis.

Methods: This prospective observational study was conducted at the Department of Paediatric Nephrology, Bangladesh Shishu Hospital & Institute, from July 2021 to June 2023, with a sample size of 28. The study utilized a non-probability sampling technique, and data were analyzed using the SPSS version 20.0 program.

Results: Patients with >50% crescentic involvement experienced gradual deterioration, requiring acute renal replacement therapy, while only 15% in the <50% crescentic group improved with conservative treatment. Overall mortality rates were 50% for IgA nephropathy, 33% for lupus nephritis, and 25% for Post Infectious Glomerulonephritis (PIGN). Improvement rates were 100% for Henoch-Schonlein purpura nephritis, 67% for lupus nephritis, and 50% for PIGN. No improvement occurred in >50% of crescentic cases, with a mortality rate of 62% and a 38% incidence of Chronic Kidney Disease (CKD). Conversely, <50% of crescentic cases showed a significant improvement rate of 65% (13/20) (p value=0.007).

Conclusion: In this study higher risk of mortality found among patient with more than 50% glomerular crescents. Additionally, it indicates that Henoch Schönlein-purpura (HSP) nephritis is associated with the most favourable clinical outcome, while the mortality rate is highest (50%) in IgA nephropathy.

Keywords: Rapidly Progressive Glomerulonephritis, IgA nephropathy, Henoch-Schönlein purpura.

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Introduction

Rapidly Progressive Glomerulonephritis (RPGN) is characterized by an acute nephritic illness with a swift decline in renal function over days to weeks, often accompanied by crescent formation on histological examination.[1] Typical symptoms include oliguria, haematuria, proteinuria, enema, and hypertension. The severity of crescent formation has been considered a crucial factor in predicting the prognosis of RPGN. While some studies propose that a higher number of crescents, especially when affecting 80% or more glomeruli, is associated with a poorer outcome[2], others argue that the underlying glomerular disease type may have a more significant impact on prognosis than the extent of crescent formation.[3] The accurate assessment of crescents in renal biopsy specimens is vital for understanding and predicting the course of RPGN in both adults and children. The perspective that the type of underlying glomerular disease plays a more crucial role in predicting the outcome of rapidly progressive glomerulonephritis (RPGN) than the extent of crescent formation has found support, especially in cases such as post-streptococcal crescentic glomerulonephritis, where excellent outcomes have been observed in many children, although some studies dispute this claim.[4-6] Nonetheless, the overall renal prognosis for patients with crescentic glomerulonephritis remains poor, with

approximately half of children diagnosed with this condition progressing to end-stage renal disease (ESRD) and some developing chronic kidney disease (CKD).[7,8] Even the presence of a single crescent in a renal biopsy can signal the potential for rapid disease progression, necessitating urgent diagnosis and prompt therapeutic intervention.[9] Although renal pathology is a valuable tool for diagnosis and predicting outcomes, its availability is limited in many developing countries. Recent years, however, have seen significant improvements in renal outcomes, with nearly 60-70% of patients exhibiting normal renal function in the long term.[10] Patients with poststreptococcal crescentic glomerulonephritis often experience spontaneous improvement. However, individuals with pauci-immune crescentic glomerulo -nephritis, membranoproliferative glomerulonephritis (MPGN), and idiopathic rapidly progressive glomerulonephritis (RPGN) generally face less favourable outcomes compared to those with Henoch-Schönlein purpura (HSP) or systemic lupus erythematosus (SLE).[11] Up to 25% of patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis may progress to end-stage renal disease (ESRD).[12] Renal outcomes are influenced by the severity of renal failure at presentation, the promptness of intervention, underlying diagnosis, and renal histology.[13] The potential for recovery is associated with the proportion of cellular or fibrous components in the crescents and the extent of tubulointerstitial scarring and fibrosis.[14] Treatment of RPGN involves two phases: induction of remission and maintenance. The maintenance phase aims to prevent further renal damage and relapses, with the duration varying based on the underlying disease. The heterogeneous presentation and suboptimal outcomes of RPGN have led to diverse immunosuppression-based treatment regimens, prompting this study to analyse the outcomes of paediatrics RPGN in the context of these complexities.

Materials and Methods

This prospective observational study took place at the Department of Paediatric Nephrology, Bangladesh Shishu Hospital & Institute. The research spanned from July 2021 to June 2023, involving a total of 28 pediatric cases displaying features of rapidly progressive glomerulonephritis as the study subjects. The inclusion criteria for this study encompassed patients aged 2 to 18 years who exhibited glomerulonephritis with characteristics of rapidly progressive glomerulonephritis (RPGN), as evidenced by a rapidly increasing serum creatinine concentration surpassing the upper limit of the age-matched normal range. Additionally, only those patients who provided informed consent were eligible for participation in the study. The exclusion criteria for this study encompassed patients with pre-renal and post-renal acute kidney injury (AKI). Patients whose renal histopathology finding did not show crescent, those who had already developed chronic kidney disease (CKD), and individuals who did not provide consent to participate in the study were also excluded from the research. In this study, a non-probability sampling technique was utilized for participant selection. Data collection done from parents or legal guardians, employing a structured questionnaire covering all relevant variables. Ethical approval was obtained from the institutional review committee collection. The comprehensive process included detailed history-taking, thorough clinical examinations, laboratory (IRC), and written consent was obtained from parents or legal guardians before data investigationns. After diagnosis treatment was started according to protocol, renal histopathology was done after clinical improvement. Patients were kept under regular follow up after discharge for 3 months to see the short time outcome. During follow up patient's weight, height, Blood pressure was measured and urine R/M/E, serum creatinine and eGFR were recorded.

Outcome were categorized according to: 1. physical findings (height, weight, pallor, blood pressure), 2. serum creatinine, 3. eGFR estimation and staging of CKD, 4. death. The study children were divided into 2 groups; RPGN with ≥50% crescent and ≤50% crescents, depending on presence of crescents in light microscopy. Etiology and outcome of the study children was observed between two groups. Subsequently, all collected data were entered into a computer and analysed using the Statistical Package for Social Science (SPSS) version 20.0. The presentation of quantitative observations was done through frequencies and percentages. Associations between variables were evaluated using Fisher's exact test for categorical variables and a one-sample t-test for continuous variables, with a significance level at $p< 0.05$.

Results

This prospective observational study enrolled a total of 28 paediatric cases exhibiting features of rapidly progressive glomerulonephritis. The majority of the participants were male, accounting for 61% of the study population, and the majority were under the age of 10 years, constituting 75%

of the cases. Furthermore, a significant proportion, 82%, of the participants were from rural areas (Table I).

During the course of this study, clinical and laboratory parameters were diligently documented on a monthly basis. The observed trend indicated gradual deterioration in the conditions of patients belonging to the group with more than 50% crescentic involvement (Table II).

Table I Demography of study subjects (N=28)

Variables	N	%
Age (years)		
2-10	21	75
11-18	07	25
Gender		
Male	17	61
Female	11	39
Residence		
Urban	05	18
Rural	25	82

Table II: Monthly follow-up of RPGN patients with >50% crescent and < 50 % crescent (N=28)

		>50% crescent; n=8 (%)			<50% crescent: n=20 (%)		
Monthly follow up (n)		**1st Month (5)**	**2nd month (4)**	**3rd month (3)**	**1st Month (19)**	**2nd month (18)**	**3rd month (17)**
Dry Weight	Gain	0(00)	0(00)	0(00)	5(26)	8(44)	9(54)
	Loss/Static	3(60)	2(50)	2(67)	9(47)	7(39)	5(30)
Oliguria		3(60)	2(50)	2(67)	5(26)	4(22)	3(17)
Blood pressure	Normal	0(00)	0(00)	0(00)	8(42)	9(50)	10(59)
	Stage-1	2(40)	2(50)	1(33)	5(26)	6(33)	5(29)
	Stage-2	3(60)	2(50)	2(67)	6(32)	3(17)	2(12)
	Absent	0(00)	0(00)	0(00)	10(52)	10(56)	12(71)
Anaemia	Mild	2(40)	3(75)	1(33)	4(22)	4(22)	3(17)
	Moderate	3(60)	1(25)	2(67)	5(26)	4(22)	2(12)
Haematuria		2(40)	1(25)	1(33)	4(22)	3(17)	2(12)
Proteinuria		1(20)	2(50)	1(33)	7(36)	4(22)	3(17)
Hypoalbuminemia		1(20)	1(25)	1(33)	5(26)	3(17)	2(12)
Raised serum creatinine		5(100)	4(100)	3(100)	4(22)	4(22)	3(17)

In terms of treatment modalities, all patients in the >50% crescentic group required acute renal replacement therapy, and none showed improvement with conservative treatment alone. In contrast, among patients in the <50% crescentic group, only 15% experienced improvement with conservative treatment alone. Additionally, all patients in both groups received intravenous pulse Methylprednisolone and intravenous Cyclophosphamide as part of their treatment (Table III).

Table III: Modalities of treatment of studied RPGN patient (N=28)

Treatment	>50% crescent n=8 (%)	<50% crescent n=20 (%)	*p*-value
Only conservative	0(00)	3(15)	0.246
IPD	2(25)	5(25)	1.000
HD	6(75)	12(60)	0.331
IPD+HD	1(12)	1(5)	0.486
Pulse MP	8(100)	20(100)	1.000
IV CP	8(100)	20(100)	1.000

IPD= Intermittent peritoneal dialysis, HD=Haemodialysis
MP= Methylprednisolone, CP=Cyclophosphamide

Outcomes based on the aetiology of the studied patients, observed that the mortality in IgA nephropathy was 50% (3 out of 6 cases), in lupus nephritis 33% (1 out of 3 cases), and in post-infectious glomerulonephritis (PIGN) 25% (3 out of 12 cases). Improvement was noted in Henoch-Schönlein purpura (HSP) nephritis with a 100% improvement rate (2 out of 2 cases), lupus nephritis showed a 67% improvement rate (2 out of 3 cases), and PIGN had a 50% improvement rate (6 out of 12 cases) (Table IV).

Table IV: Outcome according to aetiology of the studied patient (N=28)

Aetiology	Improved n=13 (46.4%)	CKD n=7 (25%)	Death n=8 (28.6%)	*p*-value
PIGN	6(50)	3(25)	3(25)	0.927
IgA Nephropathy	2(33)	1(17)	3(50)	0.423
Lupus nephritis	2(67)	0	1(33)	0.559
HSP Nephritis	2(100)	0	0	0.289
C3 Nephropathy	1(50)	1(50)	0	0.56
MPGN	0	1(50)	1(50)	0.211
FSGS	0	1(50)	0	0.211

Upon analysing the outcomes of the participants, a noteworthy observation emerged: there was a lack of improvement in patients with greater than 50% crescentic involvement. The mortality rate was found to be 62%, and the development of chronic kidney disease (CKD) was noted in 38% of patients with more than 50% crescentic group. In contrast, a statistically significant improvement was identified in 65% (13/20) of patients with less than 50% crescentic involvement (*p*-value -0.007) (Table V).

Table V: Outcome of RPGN patient (N=28)

Outcome	>50% crescent (n=8) n (%)	<50% crescent (n=20) n (%)	*p*-value
Improved (n=13)	0(0.0)	13(65)	0.007
CKD (n=7)	3(38)	4(20)	0.631
Death (n=8)	5(62)	3(15)	0.04

Discussion

In this study, the age at disease onset ranged from 2 to 18 years, with a mean age of 8.8±2.1 years.[1] The demographic characteristics revealed a predominance of male patients (61%), and the majority (75%) were children under 10 years old, with 82% residing in rural areas. These demographic patterns align with findings from a study by Dewan et al.[1]. Renal replacement therapy was required for all patients in the >50% crescentic group, and none showed improvement with conservative treatment alone. In contrast, 15% of patients in the <50% crescentic group improved with conservative treatment. All patients in both groups received intravenous pulse Methylprednisolone and intravenous Cyclophosphamide. A similar study by Haycock GB et al. demonstrated that "traditional" therapy with oral steroids, immunosuppressive drugs, and anticoagulants reduced renal mortality from 85%–90% to about 50%.[15] Pulsed methylprednisolone and plasma exchange further improved outcomes, reducing mortality to about 25%. In the present study, 13 (46%) patients achieved complete recovery from renal failure, while 7 (25%) developed chronic kidney disease (CKD), and 8 (29%) unfortunately succumbed. The notable poor outcome observed in children with IgA nephropathy contrasts with the 50% mortality rate in PIGN with crescentic transformation, as previously reported by El Husseini et al. They documented varying rates of complete recovery, ranging from 14% to 50% in children. However, it is crucial to note that these studies were conducted more than 10 years ago, and treatment protocols exhibited significant heterogeneity.[6] Mortality was particularly high in RPGN cases with >50% crescents (62%, p<0.040). Overall mortality rates were higher in IgA nephropathy with 50% crescents followed by lupus nephritis with 33% crescents and PIGN with 25% crescents. Notably, HSP nephritis exhibited the most favourable clinical outcome in this study. A study by Mosaad et al[16] similarly demonstrated that postinfectious GN was the most common aetiology of RPGN, associated with the best overall outcome compared to other aetiologies. They emphasized the importance of early intervention and detection of RPGN for preserving renal function. According to Moorani KN et al[17], the outcome of rapidly progressive glomerulonephritis (RPGN) is influenced by factors such as the severity of renal failure at presentation, promptness of intervention, and underlying renal pathology. In their study, they noted that most children with RPGN from post-infectious glomerulonephritis (PIGN) exhibit an excellent prognosis without specific treatment, with over 90% regaining normal renal function in the short-term, but with a risk of chronic kidney disease (CKD) up to 31%, especially in developing countries. In another study, at the last follow-up of 22 children, 10 had stage 5 CKD, 3 had stage 4 CKD, and 7 had a calculated glomerular filtration rate (GFR) of >60 ml/min per 1.73 m2 body surface area. Persistent proteinuria was observed in the majority (65%) of patients, and the overall outcome of crescentic glomerulonephritis in children remained poor, attributed to delayed referral and diagnosis.[1] A retrospective study by Wong W et al[18] on 27 pediatric patients with acute post-streptococcal glomerulonephritis revealed that those with crescentic glomerulonephritis had a higher tendency (72.7%) to require acute dialysis, similar to findings in this study, and experienced persistent urinary sediment abnormalities after a mean follow-up of 3.2 years. The limitation of this study lies in its single-center design and a relatively small sample size, potentially limiting the generalizability of the results to the broader population.

Conclusion

This study revealed that higher risk of mortality was found among patient with more than 50% glomerular crescents. Henoch-Schonlein Purpura (HSP) nephritis is associated with the most favourable clinical outcomes, while IgA nephropathy is linked to the highest mortality rate (50%) among the studied patients.

Recommendation

Crescentic GN should be treated as a real emergency. Greater awareness of this disease needs to be created amongst the referring paediatricians to facilitate early diagnosis and prompt treatment. Moreover, further studies should be conducted involving a large sample size and multiple centers in this context.

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