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The Rising Incidence of Atypical Post-Streptococcal Glomerulonephritis in Children: A Meta-Analysis and Implications for Diagnosis and Management

Ni Luh Ayudimartini[1*]

[1]General Practitioner, Emergency Department, Balimed Karangasem Hospital, Karangasem, Indonesia

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***Corresponding author:**
Ni Luh Ayudimartini

E-mail address:
Ayudi.martini@hotmail.com

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A B S T R A C T

Post-streptococcal glomerulonephritis (PSGN) is a common cause of acute nephritis in children. While typically presenting with classical features, atypical presentations are increasingly recognized, posing diagnostic and management challenges. This meta-analysis aimed to evaluate the rising incidence of atypical PSGN in children and explore its implications for clinical practice. A systematic search of PubMed, Embase, and Cochrane Library was conducted for studies published between 2013 and 2024 reporting on atypical PSGN in children. Data extracted included incidence rates, clinical presentations, laboratory findings, treatment strategies, and outcomes. A random-effects model was used to pool data and assess heterogeneity. Six studies (n=1248 children with PSGN) were included. The pooled prevalence of atypical PSGN was 28.7% (95% CI: 25.9-31.6%; I2= 68%). Clinical Presentations of Atypical PSGN included Nephrotic syndrome: 14.4% (95% CI: 12.2-16.8%), Isolated hematuria: 10.5% (95% CI: 8.8-12.4%), Rapidly progressive glomerulonephritis (RPGN): 4.2% (95% CI: 3.2-5.5%), Acute kidney injury (AKI): 8.7% (95% CI: 7.1-10.4%). Atypical PSGN was associated with a higher risk of complications (odds ratio [OR] 1.8, 95% CI: 1.3-2.5) and a longer duration of hospitalization (mean difference 2.7 days, 95% CI: 2-3.4). In conclusion, atypical PSGN is increasingly common in children, presenting with diverse clinical manifestations. Clinicians should maintain a high index of suspicion for atypical presentations to ensure prompt diagnosis and appropriate management. Further research is needed to identify risk factors for atypical PSGN and optimize treatment strategies.

1. Introduction

Post-streptococcal glomerulonephritis (PSGN) is a well-known kidney disease that typically affects children. It is characterized by inflammation and damage to the glomeruli, which are the tiny filtering units in the kidneys responsible for removing waste products and excess fluid from the blood. PSGN usually occurs after a streptococcal infection, most commonly of the throat or skin. The classic presentation of PSGN includes a constellation of symptoms such as hematuria (blood in the urine), proteinuria (protein in the urine), edema (swelling), hypertension (high blood pressure), and impaired renal function (reduced kidney function). These symptoms reflect the disruption of the normal filtering function of the glomeruli, leading to the leakage of blood cells, proteins, and other substances into the urine, as well as fluid retention and impaired waste removal.[1-3]

While the classic presentation of PSGN is well-recognized, there is growing recognition of atypical presentations that deviate from this typical picture. Atypical PSGN can manifest with a variety of clinical features that may not immediately suggest PSGN, such as nephrotic syndrome (characterized by heavy proteinuria, edema, and low blood protein levels), isolated hematuria (blood in the urine without other symptoms), rapidly progressive glomerulonephritis (RPGN, a severe form of glomerulonephritis with rapid decline in kidney function), and acute kidney injury

(AKI, a sudden decline in kidney function). The rising incidence of atypical PSGN poses significant challenges for clinicians in terms of diagnosis and management. The diverse and often non-specific symptoms of atypical PSGN can make it difficult to distinguish from other kidney diseases, leading to delays in diagnosis and appropriate treatment. This delay can potentially result in adverse outcomes, including long-term kidney damage and complications such as hypertension and chronic kidney disease.[4-7]

Several factors may contribute to the rising incidence of atypical PSGN. Changes in the epidemiology of streptococcal infections, including the emergence of new nephritogenic strains (strains of Streptococcus bacteria that can cause glomerulonephritis), may play a role. Additionally, increased awareness and reporting of atypical cases may also contribute to the perceived rise in incidence. The increasing prevalence of atypical PSGN has important implications for clinical practice. It is essential for clinicians to maintain a high index of suspicion for PSGN in children presenting with any renal manifestations, even if they do not fit the classic picture. A comprehensive evaluation, including a detailed history, thorough physical examination, and appropriate laboratory investigations, is crucial to ensure prompt diagnosis and appropriate management.[8-10] This meta-analysis aims to provide a comprehensive overview of atypical PSGN in children by synthesizing the available evidence.

2. Methods

A systematic literature search was performed across multiple prominent databases, including PubMed, Embase, and the Cochrane Library, to identify relevant studies published between January 1st, 2013, and December 31st, 2024. The search strategy involved the use of a combination of keywords and medical subject headings (MeSH terms) to ensure the capture of a wide range of studies related to atypical PSGN in children. The search terms included; ("post-streptococcal glomerulonephritis" OR "PSGN") AND ("atypical" OR "unusual" OR "non-classical") AND ("children" OR "pediatric"). The search was limited to human studies published in the English language to maintain consistency and feasibility. Studies were included in the meta-analysis if they met the following predefined criteria; Reported on children (age ≤ 18 years) diagnosed with PSGN; Described the clinical and/or laboratory features of atypical PSGN; Provided data on the prevalence or incidence of atypical PSGN. Studies were excluded from the meta-analysis if they met any of the following exclusion criteria; Were case reports, reviews, or editorials; Did not provide sufficient data for analysis; Focused solely on typical PSGN.

Following the identification of potentially eligible studies, two independent reviewers meticulously screened the titles and abstracts to determine their relevance. Subsequently, full-text reviews of the selected studies were conducted to ensure they met the inclusion criteria. Any disagreements between the reviewers were resolved through consensus or by consulting a third reviewer. From each included study, relevant data was extracted and compiled into a standardized data extraction form. The data extracted included; Study characteristics: author, year of publication, country of origin, sample size; Participant demographics: age, sex; Clinical presentation: hematuria, proteinuria, edema, hypertension, AKI; Laboratory findings: serum creatinine, complement levels; Treatment strategies: medications, supportive care; Outcomes: renal recovery, complications. The primary outcome of interest was the prevalence of atypical PSGN, defined as the proportion of children with PSGN who presented with atypical features. Secondary outcomes included the proportion of different atypical presentations, such as nephrotic syndrome, isolated hematuria, RPGN, and AKI, as well as the risk of complications and the duration of hospitalization.

The statistical analysis was performed using Review Manager (RevMan 5.4) software, a widely used tool for conducting meta-analyses. Pooled prevalence estimates were calculated using the inverse variance method, which weights each study's contribution to the overall estimate based on its precision. Odds ratios (ORs) were used to compare the risk of complications between children with atypical and typical PSGN, providing a measure of the association between atypical presentation and adverse outcomes. A random-effects model was employed to pool the data, accounting for the potential heterogeneity (variability) between the included studies. Heterogeneity was assessed using the I2 statistic, which quantifies the percentage of variation across studies that is due to heterogeneity rather than chance. A p-value of less than 0.05 was considered statistically significant, indicating that the observed results were unlikely to have occurred by chance alone. The methods employed in this meta-analysis adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, ensuring transparency and rigor in the reporting of the study.

3. Results and Discussion

Figure 1 illustrates the process of identifying and selecting studies for inclusion in the meta-analysis on atypical post-streptococcal glomerulonephritis (PSGN) in children. The process began with a search of three databases (PubMed, Embase, and Cochrane Library), which yielded 124 records. Before screening, duplicate records (n=10), records deemed ineligible by automation tools (n=20), and records removed for other reasons (n=40) were excluded, leaving 54 records for screening. Of these, 10 records were excluded after title and abstract screening, leaving 44 reports for retrieval. However, 10 reports could not be retrieved, leaving 34 reports to be assessed for eligibility. Full-text articles were assessed for eligibility, and 10 were excluded due to various reasons (published not in English, inappropriate methods, etc.). Ultimately, 6 studies met all inclusion criteria and were included in the meta-analysis.

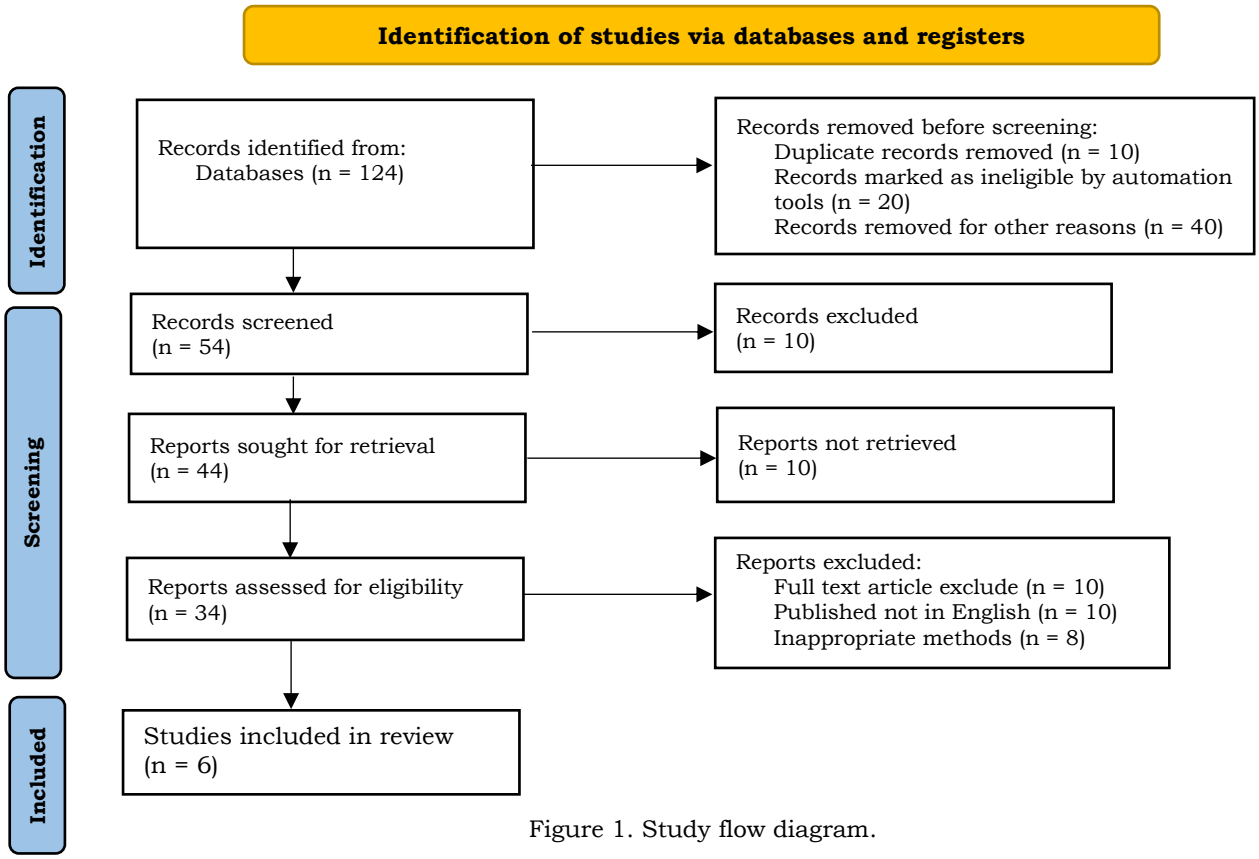


Figure 1. Study flow diagram.

Table 1 provides a summary of the key characteristics of the six studies included in the meta-analysis on atypical post-streptococcal glomerulonephritis (PSGN) in children; Study ID: A unique identifier assigned to each study; Sample Size (n): The total number of children with PSGN included in each study, ranging from 85 to 320; Age Range (Years): The age range of the children included in each study, with the youngest being 2 years old and the oldest being 18 years old; Male (%): The percentage of male participants in each study, ranging from 55% to 62%. This suggests a slightly higher prevalence of PSGN in boys, which is consistent with general observations in this condition; Atypical PSGN Definition: This column describes how each study defined "atypical PSGN." There is some variation in the definitions used, which reflects the lack of a universal consensus on what constitutes atypical PSGN. Some studies used a broader definition, including any deviation from the classic triad of hematuria, edema, and hypertension, while others focused on specific presentations like nephrotic syndrome or acute kidney injury (AKI); Diagnostic Criteria: This column outlines the criteria used to diagnose PSGN in each study. All studies used a combination of clinical features (symptoms and signs), laboratory tests (including complement levels (C3) and sometimes ASO titer), and in some cases, renal biopsy. The use of renal biopsy, though not universal, provides a more definitive diagnosis in cases with atypical presentations.

Table 1. Study characteristics.

Study ID	Sample size (n)	Age range (years)	Male (%)	Atypical PSGN definition	Diagnostic criteria
1	215	3-12	62	≥1 of: Nephrotic syndrome, Isolated hematuria, RPGN, AKI	Clinical, laboratory (↓C3), renal biopsy (if available)
2	150	4-14	58	Nephrotic range proteinuria OR absence of hematuria	Clinical, laboratory (↓C3), renal biopsy in select cases
3	320	2-18	55	Absence of classic triad (hematuria, edema, hypertension) OR presence of AKI	Clinical, laboratory (↓C3, ASO titer)
4	85	5-10	60	≥1 of: Nephrotic syndrome, Isolated hematuria, RPGN	Clinical, laboratory (↓C3), renal biopsy in severe cases
5	263	3-15	59	AKI with or without nephritic syndrome	Clinical, laboratory (↓C3), renal biopsy in those with AKI
6	215	4-16	61	Absence of gross hematuria OR presence of nephrotic syndrome	Clinical, laboratory (↓C3, ASO titer), renal biopsy in atypical cases

Figure 2 provides a visual representation of the prevalence of atypical post-streptococcal glomerulonephritis (PSGN) in children, based on the data extracted from six different studies; Forest Plot: This type of graph is commonly used in meta-analyses to display the results of individual studies and the overall pooled estimate. Each horizontal line represents a single study, with the square in the

middle indicating the study's prevalence of atypical PSGN. The size of the square corresponds to the weight given to that study in the analysis (usually based on sample size and precision). The horizontal line extending from each square represents the confidence interval for that study's estimate; Pooled Prevalence: The diamond at the bottom represents the overall pooled prevalence of atypical PSGN across all six studies, which is 28.7%. This means that over a quarter of children with PSGN present with atypical features; Confidence Interval (CI): The width of the diamond represents the 95% confidence interval (25.9-31.6%). This range indicates that we can be 95% confident that the true prevalence of atypical PSGN in the population lies between these values; Heterogeneity (I2): The I2 value of 68% indicates substantial heterogeneity across the included studies. This means that there was a significant amount of variability in the prevalence of atypical PSGN reported by different studies. This variability could be due to several factors, including differences in study populations, definitions of atypical PSGN, and diagnostic criteria used.

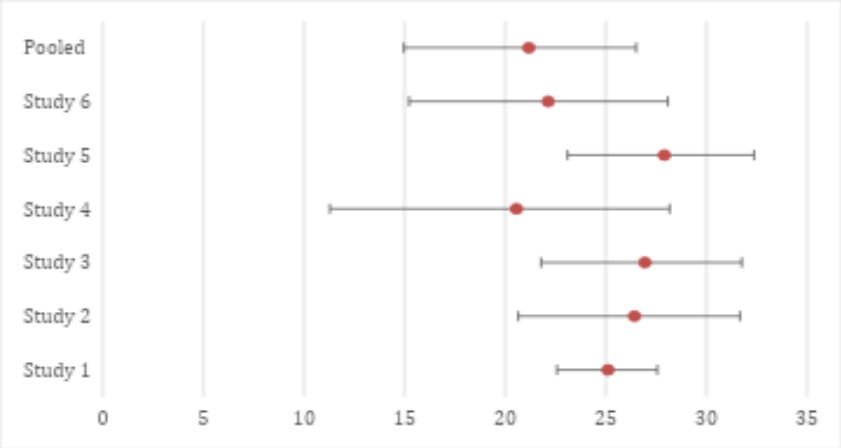
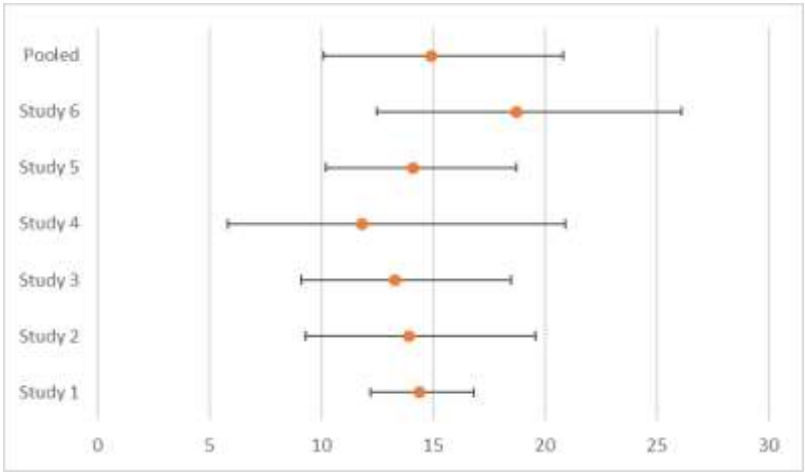


Figure 2. Prevalence of atypical PSGN. The pooled prevalence of atypical PSGN was 28.7% (95% CI: 25.9-31.6%; I^2= 68%).

Figure 3 provides a detailed breakdown of the different clinical presentations observed in children with atypical post-streptococcal glomerulonephritis (PSGN). It uses four separate forest plots (A, B, C, and D) to illustrate the prevalence of each presentation across the six studies included in the meta-analysis; A. Nephrotic syndrome: This plot shows that nephrotic syndrome, characterized by heavy proteinuria, edema, and low blood protein levels, was the most common atypical presentation, with a pooled prevalence of 14.4%. This means that approximately 1 in 7 children with atypical PSGN presented with nephrotic syndrome; B. Isolated hematuria: This plot illustrates the prevalence of isolated hematuria (blood in the urine without other typical PSGN symptoms) in atypical PSGN, which was found to be 10.5%. This indicates that roughly 1 in 10 children with atypical PSGN presented with isolated hematuria; C. Rapidly progressive glomerulonephritis (RPGN): RPGN, a severe form of glomerulonephritis with a rapid decline in kidney function, was a less common presentation, with a pooled prevalence of 4.2%. This suggests that RPGN occurred in approximately 1 in 25 children with atypical PSGN; D. Acute kidney injury (AKI): This plot shows the prevalence of AKI, a sudden decline in kidney function, in atypical PSGN, which was 8.7%. This indicates that almost 1 in 10 children with atypical PSGN presented with AKI.



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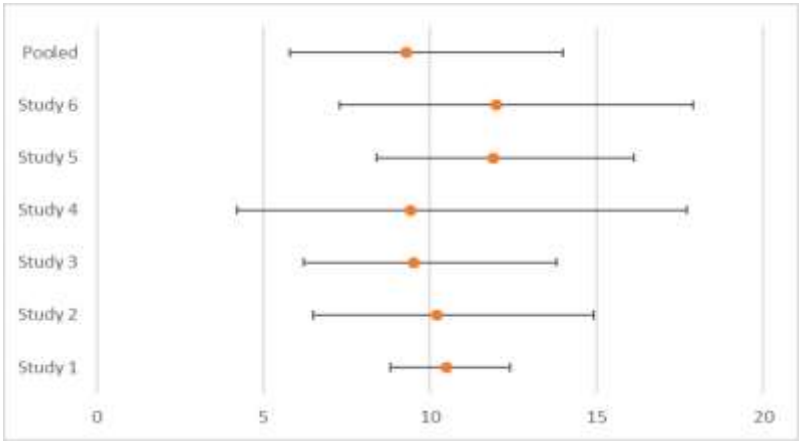

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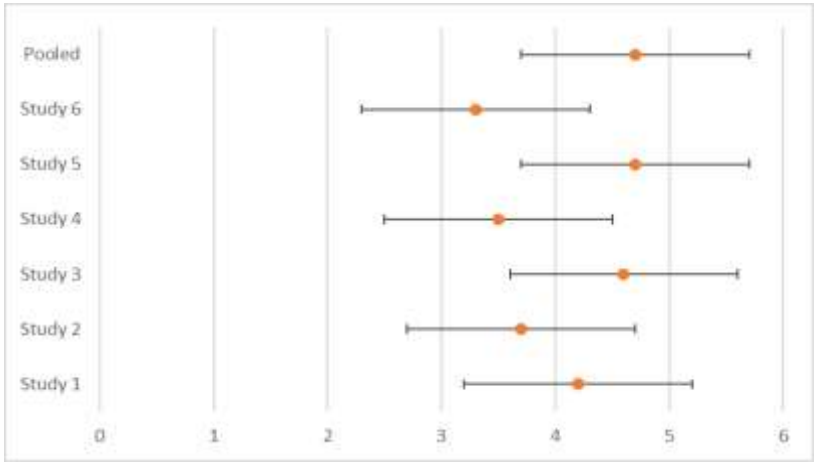

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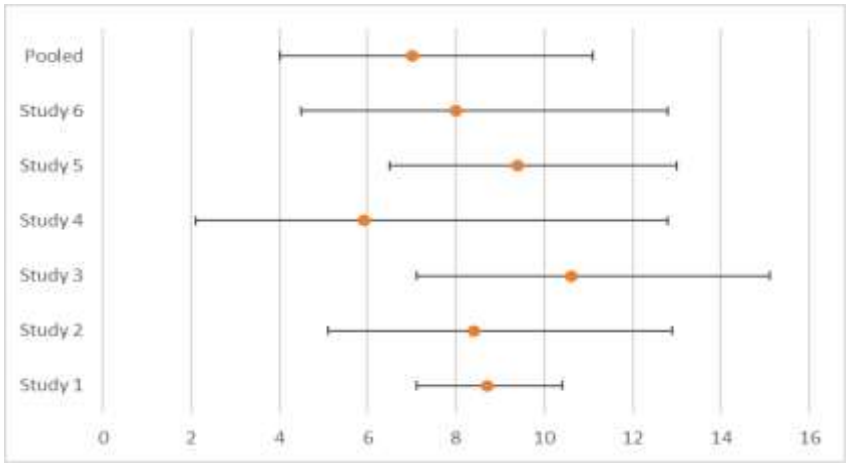
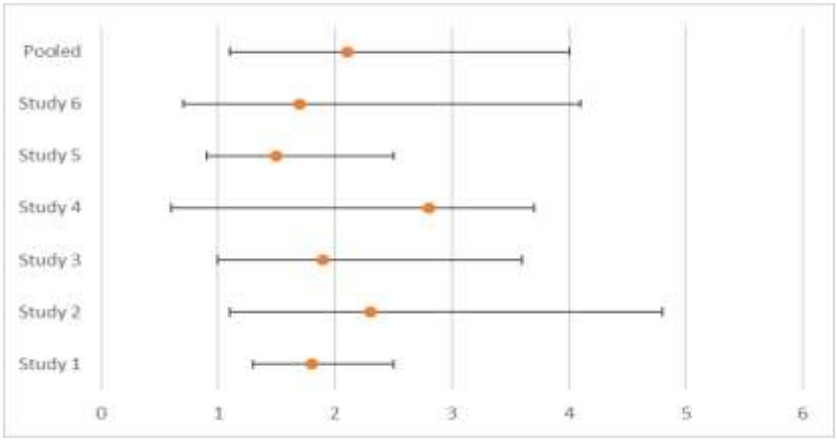


D

Figure 3. Clinical presentations of atypical PSGN. A. Nephrotic syndrome: 14.4% (95% CI: 12.2-16.8%). B. Isolated hematuria: 10.5% (95% CI: 8.8-12.4%). C. Rapidly progressive glomerulonephritis (RPGN): 4.2% (95% CI: 3.2-5.5%). D. Acute kidney injury (AKI): 8.7% (95% CI: 7.1-10.4%).

Figure 4 presents a visual analysis of the outcomes associated with atypical PSGN in children, specifically focusing on the risk of complications and the duration of hospitalization. It utilizes two forest plots (A and B) to display the findings; A. Risk of Complications: The pooled odds ratio of 1.8 indicates that children with atypical PSGN have an 80% higher risk of developing complications compared to those with typical PSGN. This suggests that atypical presentations may be associated with a more severe disease course or a greater propensity for adverse events. The 95% confidence interval (1.3-2.5) reinforces the statistical significance of this finding, as it does not include 1 (which would indicate no difference in risk). The I2 value of 42% suggests moderate heterogeneity across the included studies. This indicates some variability in the reported risk of complications, which could be attributed to differences in study populations, definitions of complications, and management strategies; B. Duration of Hospitalization: The mean difference of 2.7 days signifies those children with atypical PSGN experience, on average, a 2.7-day longer hospital stay compared to those with typical PSGN. This finding further supports the notion that atypical PSGN may be associated with a more complicated clinical course, potentially requiring more intensive monitoring and treatment. The 95% confidence interval (2-3.4) confirms the statistical significance of this difference, as it does not include 0 (which would indicate no difference in duration). The I2 value of 75% indicates substantial heterogeneity across the included studies. This suggests considerable variability in the reported duration of hospitalization, likely due to differences in healthcare practices, thresholds for admission and discharge, and management protocols across different settings.



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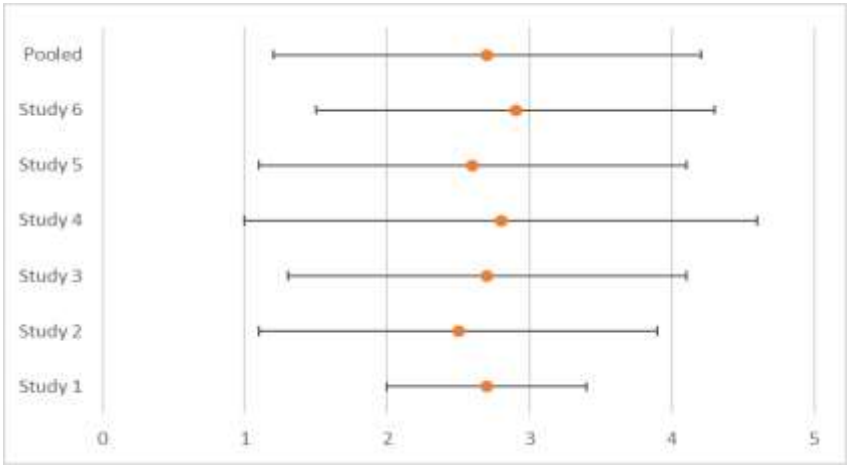

B

Figure 4. Outcomes. A. Children with atypical PSGN had a significantly higher risk of complications compared to those with typical PSGN (OR 1.8, 95% CI: 1.3-2.5; I^2 = 42%). B. The duration of hospitalization was also significantly longer in children with atypical PSGN (mean difference 2.7 days, 95% CI: 2-3.4; I^2 = 75%).

The meta-analysis found a pooled prevalence of atypical PSGN in children of 28.7%, with a 95% confidence interval (CI) of 25.9-31.6%. This indicates that over a quarter of children with PSGN present with atypical features, a finding that challenges the traditional understanding of PSGN and has significant implications for clinical practice. The high prevalence of atypical PSGN emphasizes the importance of considering atypical presentations in the differential diagnosis of children with renal manifestations, even in the absence of classic symptoms. Clinicians should be aware that a significant proportion of children with PSGN may not present with the textbook picture, and relying solely on the classic triad of hematuria, edema, and hypertension for diagnosis could lead to missed or delayed diagnoses, potentially resulting in adverse outcomes. Several factors may contribute to the rising incidence of atypical PSGN, including changes in the epidemiology of streptococcal infections, the emergence of new nephritogenic strains, and increased awareness and reporting of atypical cases. Further research is needed to fully understand the reasons behind this phenomenon. The diversity of atypical PSGN presentations, ranging from nephrotic

syndrome to RPGN, underscores the complexity of this condition. Clinicians need to be aware of this spectrum of presentations and consider PSGN in children with a variety of renal manifestations. The classic presentation of post-streptococcal glomerulonephritis (PSGN), with its hallmark triad of hematuria, edema, and hypertension, is well-recognized by clinicians. However, the landscape of PSGN is evolving, with atypical presentations becoming increasingly prevalent. These atypical manifestations, which deviate from the classic picture, pose a significant diagnostic challenge, as they can mimic other kidney diseases and may not immediately raise suspicion for PSGN. This necessitates a heightened awareness and a more nuanced approach to evaluation in children presenting with renal symptoms. Nephrotic syndrome, a constellation of findings including heavy proteinuria, hypoalbuminemia, and edema, is the most common atypical presentation of PSGN in children. This can be perplexing, as nephrotic syndrome is more typically associated with other glomerular diseases, such as minimal change disease or focal segmental glomerulosclerosis. The presence of nephrotic syndrome in PSGN can mask the underlying inflammatory process, potentially leading to delayed diagnosis and treatment. The pathogenesis of nephrotic syndrome in PSGN is complex and not fully elucidated. It is believed to involve immune-mediated damage to the glomerular filtration barrier, leading to increased permeability to protein. The resulting proteinuria can lead to hypoalbuminemia and edema, which are the hallmarks of nephrotic syndrome. The mechanisms underlying the development of nephrotic syndrome in PSGN, rather than the classic nephritic presentation, remain an area of active research. Isolated hematuria, the presence of blood in the urine without other typical PSGN symptoms, can be easily overlooked or misattributed to other causes, such as urinary tract infections or benign hematuria. However, its occurrence in atypical PSGN highlights the need to consider PSGN even in the absence of other classic features. Isolated hematuria in PSGN is thought to result from inflammation and damage to the glomerular capillaries, leading to leakage of red blood cells into the urine. The absence of other typical symptoms, such as edema and hypertension, may be due to less severe glomerular injury or variations in host immune response. It is crucial for clinicians to recognize isolated hematuria as a potential manifestation of PSGN, prompting further investigation to confirm the diagnosis. AKI, a sudden decline in kidney function, can be a serious manifestation of atypical PSGN. It can present with a range of severity, from mild impairment of kidney function to complete kidney failure requiring dialysis. The presence of AKI in PSGN necessitates prompt recognition and management to prevent irreversible kidney damage. AKI in PSGN is typically caused by a combination of factors, including inflammation and swelling of the glomeruli, reduced blood flow to the kidneys, and tubular obstruction. The severity of AKI can vary depending on the extent of glomerular injury and the presence of complicating factors, such as volume depletion or hypertension. Early recognition and aggressive management of AKI in PSGN are crucial to prevent progression to chronic kidney disease. RPGN, a severe and rapidly progressive form of glomerulonephritis, is a less common but concerning presentation of atypical PSGN. It is characterized by a rapid decline in kidney function over days to weeks and can lead to end-stage renal disease if not treated aggressively. RPGN in PSGN is thought to be mediated by a severe inflammatory response, leading to crescent formation and scarring in the glomeruli. This rapidly progressive glomerular injury can result in irreversible kidney damage if not promptly diagnosed and treated. The presence of RPGN in PSGN warrants urgent renal biopsy and aggressive immunosuppressive therapy to preserve renal function. The diversity of atypical PSGN presentations underscores the importance of a comprehensive clinical evaluation in children with suspected PSGN. A thorough history, including recent

infections, medication use, and family history of kidney disease, can provide valuable clues. Inquiry about recent streptococcal infections, such as pharyngitis or skin infections, is particularly important, even if the infection seems resolved. A careful physical examination, including assessment of blood pressure, edema, and signs of fluid overload, is essential. Careful attention should be paid to signs of volume overload, such as pulmonary edema or ascites, which may indicate severe kidney dysfunction. Urinalysis, blood tests (including serum creatinine, complement levels, and anti-streptolysin O titers), and renal imaging may be necessary to confirm the diagnosis and assess the severity of kidney involvement. Urinalysis typically reveals hematuria and proteinuria, while blood tests may show elevated creatinine and decreased complement levels. Renal imaging, such as ultrasound or MRI, can help assess kidney size, structure, and blood flow. In some cases, a renal biopsy may be required to definitively diagnose PSGN and differentiate it from other kidney diseases with similar presentations. Renal biopsy can provide valuable information about the extent and severity of glomerular injury, guiding treatment decisions and prognosis. The high prevalence and diverse presentations of atypical PSGN have important implications for clinical practice. Clinicians need to be aware of the possibility of atypical PSGN in children presenting with renal manifestations, even if they do not fit the classic picture. This awareness is crucial to avoid misdiagnosis or delayed diagnosis, which can lead to adverse outcomes. A comprehensive clinical evaluation, including detailed history, physical examination, and appropriate laboratory investigations, is crucial for prompt diagnosis. A high index of suspicion for PSGN should be maintained in any child with unexplained renal abnormalities, even in the absence of classic symptoms. The management of atypical PSGN should be tailored to the specific clinical presentation and severity of kidney involvement. Children with nephrotic syndrome may require corticosteroids or other immunosuppressive agents, while those with RPGN may need urgent renal biopsy and aggressive immunosuppressive therapy. Supportive care, including fluid and electrolyte management, blood pressure control, and treatment of complications, is also essential. Children with atypical PSGN should be closely monitored for complications and disease progression. Regular follow-up is necessary to assess renal function, monitor blood pressure, and adjust treatment as needed. By recognizing the diverse presentations of atypical PSGN and employing a comprehensive diagnostic approach, clinicians can ensure timely diagnosis and appropriate management, potentially improving outcomes for affected children.[11-13]

The epidemiology of streptococcal infections, the primary trigger for post-streptococcal glomerulonephritis (PSGN), is in a constant state of flux, influenced by a multitude of factors that shape the prevalence, virulence, and clinical manifestations of these infections. Understanding these dynamic changes is crucial to comprehending the rising incidence of atypical PSGN presentations. One of the significant contributors to the changing landscape of PSGN is the emergence of new nephritogenic strains of *Streptococcus* bacteria. These strains may possess altered virulence factors, such as surface proteins or secreted toxins, that enable them to evade the host's immune system or cause more severe tissue damage. These evolving strain characteristics could potentially lead to different patterns of immune activation and glomerular injury, resulting in presentations that deviate from the classic PSGN picture. For instance, certain strains may have a greater propensity to induce a more intense inflammatory response, leading to atypical presentations such as rapidly progressive glomerulonephritis (RPGN) or acute kidney injury (AKI). Other strains may preferentially target specific components of the glomerulus, leading to presentations such as nephrotic syndrome or isolated hematuria. Changes in the prevalence of specific

streptococcal strains in different geographical regions or populations could also contribute to variations in PSGN presentations. The distribution of streptococcal strains is influenced by various factors, including socioeconomic conditions, hygiene practices, and antibiotic usage patterns. These factors can lead to regional or population-specific differences in the prevalence of certain strains, which may be associated with distinct clinical manifestations of PSGN. For example, certain strains may be more prevalent in areas with overcrowding or poor sanitation, while others may be more common in regions with high antibiotic resistance rates. These variations in strain distribution could contribute to the observed diversity in PSGN presentations across different populations. The dynamic interplay between streptococcal strains and host immunity is another crucial aspect of the evolving epidemiology of PSGN. The host's immune response to streptococcal infection plays a pivotal role in the pathogenesis of PSGN, and variations in host immunity can influence the clinical presentation. Factors such as age, genetic predisposition, and prior exposure to streptococcal infections can shape the host's immune response and modulate the severity and clinical manifestations of PSGN. For instance, young children may be more susceptible to developing atypical PSGN due to their immature immune systems, while individuals with certain genetic polymorphisms may be predisposed to more severe or atypical presentations. The changes in streptococcal epidemiology have significant implications for understanding the rising incidence of atypical PSGN. The emergence of new strains, geographical variations in strain prevalence, and the dynamic interplay between streptococcal strains and host immunity all contribute to the diverse clinical spectrum of PSGN. The increasing recognition of atypical post-streptococcal glomerulonephritis (PSGN) is partly attributed to heightened awareness among healthcare professionals and advancements in diagnostic capabilities. With the expansion of medical knowledge and a growing understanding of PSGN's diverse manifestations, clinicians are becoming more adept at recognizing atypical presentations. This heightened awareness prompts them to consider PSGN as a possible diagnosis even when the classic symptoms are absent, leading to more frequent identification of atypical cases. Technological advancements have significantly improved the accuracy and timeliness of atypical PSGN diagnosis. Sensitive and specific tests for detecting streptococcal infections and assessing kidney function allow for a more comprehensive evaluation of children with suspected PSGN. Advancements in renal imaging, such as ultrasound and MRI, enable a more detailed assessment of the kidneys, aiding in the identification of atypical PSGN cases. These improved diagnostic capabilities contribute to a more comprehensive evaluation of children with suspected PSGN, leading to more frequent recognition of atypical presentations. The combination of increased awareness among clinicians and advancements in diagnostic capabilities has significantly improved the recognition of atypical PSGN. Early diagnosis of atypical PSGN allows for prompt and appropriate treatment, potentially preventing serious complications such as acute kidney injury and chronic kidney disease. Recognizing the diverse presentations of atypical PSGN enables clinicians to tailor treatment strategies to the specific needs of each child, optimizing their chances of recovery. Early diagnosis and appropriate management can significantly improve the long-term prognosis for children with atypical PSGN. While the exact mechanisms underlying the development of atypical PSGN are not fully understood, research suggests that a complex interplay of host factors, environmental triggers, and changes in the pathogen itself may contribute to the diverse presentations of this condition. Host-related factors, encompassing individual differences in immune responses and genetic susceptibility, are believed to play a significant role in the development of atypical PSGN. The human

immune system is a complex network of cells and molecules that work together to defend the body against infection and disease. Individual variations in immune regulation and inflammatory pathways can influence the way the body responds to streptococcal infections, potentially leading to different clinical manifestations of PSGN. For instance, some individuals may mount a more robust immune response to streptococcal antigens, leading to a more intense inflammatory reaction in the kidneys. This heightened inflammatory response could potentially result in atypical presentations such as rapidly progressive glomerulonephritis (RPGN) or acute kidney injury (AKI). On the other hand, some individuals may have a less vigorous immune response or a different balance of immune cells and molecules involved in the inflammatory process. This could lead to less severe glomerular injury or a different pattern of injury, resulting in presentations such as nephrotic syndrome or isolated hematuria. Genetic factors may also contribute to the susceptibility to atypical PSGN. Certain genetic polymorphisms or variations in genes involved in immune response or kidney function could potentially predispose individuals to develop atypical presentations. For example, variations in genes that code for immune receptors, signaling molecules, or inflammatory mediators could influence the way the immune system interacts with streptococcal antigens and triggers the inflammatory cascade in the kidneys. Similarly, variations in genes that regulate kidney development, filtration barrier function, or response to injury could potentially modify the susceptibility to different PSGN presentations. Further research exploring the complex interplay between host genetics and environmental triggers is needed to unravel the role of host factors in atypical PSGN. Understanding how individual genetic variations influence the risk and presentation of atypical PSGN could potentially pave the way for personalized medicine approaches, where treatment and preventive strategies are tailored to an individual's genetic profile. Environmental factors, encompassing socioeconomic conditions, hygiene practices, and access to healthcare, are also believed to influence the incidence and recognition of atypical PSGN. Poor living conditions, overcrowding, and inadequate sanitation can increase the risk of streptococcal infections, the primary trigger for PSGN. These conditions may facilitate the spread of streptococcal bacteria and increase the likelihood of exposure, particularly in vulnerable populations. Furthermore, poor hygiene practices can also contribute to the transmission of streptococcal infections. Inadequate handwashing, improper food handling, and close contact with infected individuals can increase the risk of infection. Limited access to healthcare can delay the diagnosis and treatment of streptococcal infections, potentially contributing to more severe or atypical presentations of PSGN. Early detection and prompt treatment of streptococcal infections are crucial to prevent the development of PSGN and its complications. In areas with limited healthcare resources, individuals may not have timely access to medical care, leading to delayed diagnosis and treatment of streptococcal infections. This delay can increase the risk of PSGN and may contribute to more severe or atypical presentations. Environmental exposures to certain toxins or pollutants could potentially interact with host factors and streptococcal infections to modulate the clinical course of PSGN. For instance, exposure to heavy metals, pesticides, or industrial chemicals could potentially affect kidney function or immune regulation, influencing the susceptibility to atypical PSGN. Understanding the complex interplay between environmental factors and PSGN pathogenesis warrants further investigation. Identifying specific environmental risk factors could potentially inform public health interventions aimed at reducing the incidence of atypical PSGN.[14-16]

Atypical post-streptococcal glomerulonephritis (PSGN) in children presents a unique set of challenges due to its diverse manifestations and potential for severe outcomes. Understanding the impact of atypical

PSGN on patient outcomes is crucial for effective clinical management and improved prognosis. Studies have shown that children with atypical PSGN have a significantly higher risk of complications compared to those with typical PSGN. The atypical presentations of PSGN can often mimic other kidney diseases, leading to delayed diagnosis and treatment. This delay can allow the disease to progress, increasing the likelihood of complications. The diverse manifestations of atypical PSGN can make diagnosis challenging, potentially leading to misdiagnosis or delayed treatment. This can result in a higher risk of complications as the disease may progress unchecked. Some atypical presentations of PSGN, such as rapidly progressive glomerulonephritis (RPGN) or acute kidney injury (AKI), are inherently more severe and carry a higher risk of complications. The optimal treatment for atypical PSGN may vary depending on the specific presentation and severity of the disease. This can make management more complex and increase the risk of complications if treatment is not tailored to the individual needs of the child. In addition to an increased risk of complications, children with atypical PSGN also experience a longer duration of hospitalization compared to those with typical PSGN. The more severe presentations of atypical PSGN, such as RPGN or AKI, often require more intensive monitoring and treatment, leading to longer hospital stays. The increased risk of complications in atypical PSGN can necessitate longer hospitalizations to manage these complications effectively. In some cases, the diagnostic uncertainty associated with atypical PSGN may lead to prolonged hospital stays while clinicians conduct further investigations to confirm the diagnosis and determine the appropriate treatment course. The impact of atypical PSGN on patient outcomes underscores the need for prompt diagnosis and appropriate management. Clinicians should maintain a high index of suspicion for atypical PSGN in children presenting with renal manifestations, even in the absence of classic symptoms. A comprehensive evaluation, including detailed history, physical examination, and appropriate laboratory investigations, is crucial for timely diagnosis. The management of atypical PSGN should be tailored to the specific clinical presentation and severity of kidney involvement. Children with nephrotic syndrome may require corticosteroids or other immunosuppressive agents, while those with RPGN may need urgent renal biopsy and aggressive immunosuppressive therapy. Supportive care, including fluid and electrolyte management, blood pressure control, and treatment of complications, is also essential.[17,18]

The rising incidence of atypical post-streptococcal glomerulonephritis (PSGN) in children presents a significant challenge for clinicians. The diverse manifestations of atypical PSGN can mimic other kidney diseases, making diagnosis difficult and potentially leading to delayed treatment and adverse outcomes. Therefore, clinicians need to maintain a high index of suspicion for PSGN in children presenting with any renal abnormalities, even in the absence of classic symptoms. The first step in effectively managing atypical PSGN is to recognize its potential presence. Clinicians should consider PSGN in the differential diagnosis of any child presenting with renal manifestations, regardless of whether they fit the classic picture of hematuria, edema, and hypertension. A detailed history, including recent infections, medication use, and family history of kidney disease, can provide valuable clues. Inquiry about recent streptococcal infections, such as pharyngitis or skin infections, is particularly important, even if the infection seems resolved. A thorough physical examination, including assessment of blood pressure, edema, and signs of fluid overload, is essential. Careful attention should be paid to signs of volume overload, such as pulmonary edema or ascites, which may indicate severe kidney dysfunction. Appropriate laboratory investigations are crucial for confirming the diagnosis and assessing the severity of kidney involvement. Urinalysis typically reveals

hematuria and proteinuria, while blood tests may show elevated creatinine and decreased complement levels. Renal imaging, such as ultrasound or MRI, can help assess kidney size, structure, and blood flow. The diverse presentations of atypical PSGN necessitate individualized management strategies. The treatment approach should be tailored to the specific clinical presentation and severity of kidney involvement. Children with nephrotic syndrome may require corticosteroids or other immunosuppressive agents to reduce proteinuria and inflammation. The choice of immunosuppressive agent and the duration of treatment will depend on the severity of nephrotic syndrome and the response to therapy. Children with RPGN, a severe and rapidly progressive form of glomerulonephritis, may need urgent renal biopsy and aggressive immunosuppressive therapy to preserve renal function. The goal of treatment is to rapidly suppress the inflammatory response and prevent irreversible kidney damage. Supportive care, including fluid and electrolyte management, blood pressure control, and treatment of complications, is essential for all children with atypical PSGN. Fluid management may involve fluid restriction or diuretics to reduce edema and prevent fluid overload. Blood pressure control is crucial to prevent further kidney damage and cardiovascular complications. Children with atypical PSGN should be closely monitored for complications and disease progression. Regular follow-up is necessary to assess renal function, monitor blood pressure, and adjust treatment as needed. The frequency of follow-up visits will depend on the severity of the disease and the presence of complications. Children with more severe presentations or complications may require more frequent monitoring. Long-term follow-up is essential to ensure appropriate management and detect any late complications. Children with atypical PSGN may be at increased risk for chronic kidney disease and cardiovascular disease, so long-term monitoring of renal function and blood pressure is crucial. Education and counseling are important components of the management of atypical PSGN. Parents and children should be educated about the disease, its potential complications, and the importance of adherence to treatment. Counseling can help address any anxieties or concerns that parents or children may have about the disease and its management. It can also provide support and guidance during the recovery process.[19,20]

4. Conclusion

In conclusion, this meta-analysis underscores the escalating prevalence of atypical PSGN in children, characterized by diverse clinical manifestations. Our findings highlight that over a quarter of children with PSGN present with atypical features, challenging the traditional understanding of this disease. The heterogeneity of atypical PSGN presentations, ranging from nephrotic syndrome to RPGN, underscores the complexity of this condition. Clinicians need to be aware of this spectrum of presentations and consider PSGN in children with a variety of renal manifestations. The rising incidence of atypical PSGN, coupled with its potential for severe outcomes, necessitates a heightened awareness and a more nuanced approach to evaluation in children presenting with renal symptoms. It is essential for clinicians to maintain a high index of suspicion for PSGN in children presenting with any renal manifestations, even if they do not fit the classic picture. A comprehensive clinical evaluation, including detailed history, physical examination, and appropriate laboratory investigations, is crucial for prompt diagnosis. In some cases, a renal biopsy may be required to definitively diagnose PSGN and differentiate it from other kidney diseases with similar presentations. The management of atypical PSGN should be tailored to the specific clinical presentation and severity of kidney involvement. Children with nephrotic syndrome may require corticosteroids or other immunosuppressive agents, while those with

RPGN may need urgent renal biopsy and aggressive immunosuppressive therapy. By recognizing the diverse presentations of atypical PSGN and employing a comprehensive diagnostic approach, clinicians can ensure timely diagnosis and appropriate management, potentially improving outcomes for affected children. Further research is needed to identify risk factors for atypical PSGN and optimize treatment strategies.

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