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Profile and outcome of atypical progressive acute kidney injury in children in a tertiary care hospital in Indonesia

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Original Article

ABSTRACT

Background: Atypical progressive acute kidney injury (APAKI) in children is a severe form of acute kidney injury (AKI) marked by rapid progression to end-stage and high mortality. Since August 2022, Indonesia has reported a surge of pediatric AKI, predominantly in previously healthy children, linked to contamination of syrup medications with diethylene glycol (DEG) and ethylene glycol (EG).
Objective: The objective of this research is to identify the characteristics and clinical outcomes of children with APAKI at Dr. Zainoel Abidin Hospital in Banda Aceh, a tertiary care hospital in Indonesia.
Methods: This analytical observational study used secondary data from pediatric medical records of APAKI cases between June and December 2022. A total sampling technique identified 31 eligible patients aged 1–18 years old. Clinical characteristics, laboratory parameters, and outcomes were analyzed using descriptive statistics and Fisher's Exact tests.
Results: Thirty-one pediatric patients with APAKI are included; most are male (64.5%), aged 1–5 years (93.5%), domiciled outside Banda Aceh (58.1%), and had good nutritional status (80.6%). The mortality is high (74.2%). Genitourinary symptoms such as oliguria/anuria are the most frequent (87.1%), and dialysis is the main therapy (64.5%). Poor outcomes are significantly associated with respiratory symptoms (OR=16; 95%CI: 1.643-155.77), PELOD-2 score ≥10 (OR=10.89; 95%CI: 1.140-103.98), and mechanical ventilation (OR=16; 95%CI: 1.643-155.77). Laboratory predictors of mortality included leukocytosis (OR=11.11; 95%CI: 1.701-72.564), thrombocytopenia (OR=1.90; 95%CI: 1.207-2.957), elevated urea (OR=13.2; 95%CI: 1.124-154.920), elevated creatinine (OR=36.67; 95%CI: 3.124-430.333), reduced eGFR (OR=22; 95%CI: 1.924-251.539), and elevated SGOT (OR=22; 95%CI: 1.924-251.539) and SGPT (OR=36.67; 95%CI: 3.124-430.333). Toxicology testing is correlated with better survival (OR=0.07; 95% CI: 0.006-0.889).
Conclusion: APAKI in children is associated with high mortality. Poor outcomes are strongly linked to respiratory involvement, high PELOD-2 scores, mechanical ventilation, and multiple laboratory abnormalities, highlighting the importance of early risk identification and timely management.

INTRODUCTION

Acute Kidney Injury (AKI) refers to a sudden impairment of renal function in maintaining fluid and electrolyte homeostasis, indicated by an abrupt decline in glomerular filtration rate (GFR). This disorder is typically accompanied by elevated serum urea and creatinine levels (exceeding 50% of normal values) and, in certain cases, decreased urine output (<0.5–1 mL/kgBW/hour).[1]

Globally, one in every critically ill child develops AKI, which significantly affects clinical outcomes. Progression to kidney failure may lead to the need for renal replacement therapy, persistent renal dysfunction, or even death.[2] A systematic review by Meena et al in 2023 reported that the global incidence of AKI in hospitalized children reached 26%, with 11% requiring dialysis

and 11% experiencing mortality.[3] Weiss et al. reported, based on a retrospective method, that among patients with stage 2 and 3 AKI, 4.5% required renal replacement therapy, 4.5% died, and 5.8% suffered persistent renal dysfunction.[4] A large multinational prospective study also showed that pediatric AKI is quite common, particularly among children undergoing cardiac surgery and intensive care, with an incidence of 26.9%, and 30–50% in post-operative cases.[3] In Indonesia, Hidayati et al. reported a significant increase in pediatric AKI cases since August 2022 across several regions, including Java, Bali, Sumatra, Kalimantan, Sulawesi, East Nusa Tenggara, and West Papua.[5] These cases were predominantly seen in previously healthy children without an existing record of chronic kidney disorder.[5,6] The Indonesian Ministry of Health (*Kementerian Kesehatan,* Kemenkes) also reported Aceh as one of the provinces with a yearly increase in AKI cases, which were later classified as Atypical progressive acute kidney injury (APAKI).[7] These cases were typically preceded by fever, gastrointestinal, and respiratory symptoms within two weeks of diagnosis, with no prior history of renal disorders.[6]

The initial treatment of APAKI followed standard protocols for Multisystem Inflammatory Syndrome in Children (MIS-C), involving the use of corticosteroids, immunoglobulins, anticoagulants, and dialysis. Nevertheless, this strategy did not result in improved clinical outcomes and remained linked to a persistently high mortality rate (>50%), even among patients who underwent dialysis.[6] As of February 5, 2023, the World Health Organization (WHO) reported over 300 APAKI cases, with more than half resulting in death. Diethylene glycol (DEG) and ethylene glycol (EG) exposure was identified as the primary etiology, following similar outbreaks in Gambia in 2022.[8] Both chemicals are known to cause systemic intoxication and can mimic the clinical manifestations of MIS-C, with multi-organ involvement including AKI and elevated anion gap type of metabolic acidosis.[6] According to investigations by the Indonesian Ministry of Health and Indonesian Pediatric Society (*Ikatan Dokter Anak Indonesia*, IDAI), DEG/EG was detected in 42.2% of tested syrup formulations and in 60.3% of plasma samples from affected patients. Further analysis by the Indonesian Food and Drug Authority (BPOM) confirmed contamination in five syrup products, which were subsequently withdrawn from circulation.[8]

Aceh continues to report a high incidence of APAKI, yet comprehensive data on the clinical features and outcomes of affected children in this region are lacking. This study was conducted to assess the clinical, laboratory, and outcome characteristics of pediatric APAKI cases managed at Dr. Zainoel Abidin General Hospital, Banda Aceh. The findings are expected to provide scientific insights for improving the understanding and management of APAKI in Indonesia, as well as inform national health policies aimed at preventing nephrotoxic exposures in children.

METHODS

Study design

This study employed an analytical observational design with a retrospective approach to evaluate the clinical characteristics and outcomes of pediatric patients with atypical progressive acute kidney injury (APAKI). The study was conducted at Dr. Zainoel Abidin General Hospital, Banda Aceh, a tertiary care hospital. Data collection was carried out between June and August 2024 using medical records of patients treated from June to December 2022.

Population and sample

The target population comprised all pediatric patients diagnosed with APAKI, while the accessible population included those managed at Dr. Zainoel Abidin General Hospital during the study period. Subjects were selected using a total sampling technique. Inclusion criteria were children aged 1–18 years with a diagnosis of APAKI. APAKI was operationally defined as acute kidney injury based on the Kidney Disease: Improving Global Outcomes (KDIGO) criteria (increase in serum creatinine and/or decreased urine output), with no prior history of kidney disease, rapid clinical progression, minimal response to supportive therapy, and a history of suspected or confirmed exposure to contaminated medications. Patients were excluded if their medical records were incomplete, particularly lacking key data on clinical manifestations,

laboratory findings, or outcomes. A total of 31 eligible patients met the inclusion criteria and were included in the analysis.

Data collection

Data were obtained from medical records that fulfilled the eligibility criteria and were subsequently coded and organized for analysis. The primary outcome variable was patient outcome (survival or mortality). Independent variables included demographic characteristics (age, sex, and residence), clinical features (presenting symptoms, nutritional status, and comorbidities), severity of illness assessed using the Pediatric Logistic Organ Dysfunction-2 (PELOD-2) score, laboratory parameters (hemoglobin, leukocyte count, platelet count, urea, creatinine, estimated glomerular filtration rate (eGFR), SGPT, C-reactive protein (CRP), and procalcitonin, as well as exposure and management variables, including history of medication consumption, toxicology testing, pharmacological therapy, dialysis, and mechanical ventilation. Nutritional status was assessed using anthropometric indices based on the World Health Organization (WHO) Child Growth Standards for children aged 0–5 years and the Centers for Disease Control and Prevention (CDC) growth references for those aged 5–18 years. Laboratory values were recorded based on initial measurements at hospital admission.

The operational definitions of clinical variables were adapted from the Indonesian Ministry of Health guidelines on APAKI management. Fever was defined as a body temperature ≥37.5°C or a history of fever within the preceding 14 days. Neurological symptoms were defined as decreased level of consciousness, behavioral changes, or seizures. Gastrointestinal symptoms included diarrhea, vomiting, and abdominal pain. Respiratory symptoms comprised cough, rhinorrhea, shortness of breath, and respiratory failure. Genitourinary symptoms were defined based on the patient's diuresis status, categorized as oliguria (urine output <0.5–1 mL/kg/hour in children) or anuria (absence of urine output). Comorbidities is defined as the presence of two or more coexisting medical conditions before hospital admission, including but not limited to congenital anomalies, immunological disorders, chronic kidney disease, dengue infection, malignancy, COVID-19, and typhoid fever.

Data analysis

Data analysis began with descriptive statistics for univariate evaluation. Categorical variables were summarized as frequencies and percentages, while numerical data were expressed as mean ± standard deviation for normally distributed values or as median with range for non-normal distributions. Normality was tested using the Shapiro–Wilk method, where $p>0.05$ signified a normal distribution. Bivariate relationships between categorical predictors and patient outcomes were examined using Fisher's Exact test, considering the asymmetric distribution of the data due to a small number of samples, with cell counts <5. Statistical significance was set at $p<0.05$ with 95% confidence intervals (CI). Associations were quantified using odds ratios (OR), interpreted as risk factors when OR>1, no effect when OR=1, and protective when OR<1. Data analysis was performed using SPSS version 24.

Ethical statement

The study protocol was reviewed and approved by the Ethics Committee of the Faculty of Medicine, Syiah Kuala University in conjunction with Dr. Zainoel Abidin General Hospital, Banda Aceh, under approval number 236/ETIK-RSUDZA/2024.

RESULTS

This study analyzed 31 pediatric cases of APAKI admitted to Dr. Zainoel Abidin General Hospital between June and December 2022. As shown in Table 1, most patients are male (64.5%), within the 1–5 year age group (93.5%), and residing outside Banda Aceh (58.1%). The majority presented with good nutritional status (80.6%); however, mortality remains high, with (74.2%) of patients not surviving.

Table 1. Distribution of baseline characteristics of APAKI pediatric patients (n = 31)

Characteristic	n	(%)
Sex		
Male	20	64.5
Female	11	35.5
Age group		
1–5 years	29	93.5
>5–18 years	2	6.5
Residence		
Banda Aceh	13	41.9
Other Districts	18	58.1
Nutritional status		
Normal	25	80.6
Undernourished	6	19.4
Outcome		
Survived	8	25.8
Died	23	74.2

Most patients presented with fever (80.6%), followed by gastrointestinal symptoms (61.3%), respiratory symptoms (54.8%), and neurological symptoms (25.8%). Genitourinary symptoms were observed in (87.1%) of patients. Comorbidities are not found in (87.1%) of cases. The number of patients with PELOD-2 scores <10 and ≥10 is nearly equal, with (51.6%) and (48.4%), respectively. Toxicology testing is not performed in (87.1%) of cases (Table 2).

Table 2. Distribution of APAKI patients based on clinical profile (n=31)

Clinical profile	n	%
Fever		
Yes	25	80.6
No	6	19.4
Neurological symptoms		
Yes	8	25.8
No	23	74.2
Gastrointestinal symptoms		
Yes	19	61.3
No	12	38.7
Respiratory symptoms		
Yes	17	54.8
No	14	45.2
Genitourinary symptoms		
Yes	27	87.1
No	4	12.9
Comorbidities		
Yes	4	12.9
No	27	87.1
PELOD-2 Score		
≥ 10	15	48.4
< 10	16	51.6
Toxicology examination		
Yes	4	12.9
No	27	87.1
Length of stay		
≥ 3 days	23	74.2
< 3 days	8	25.8

The analysis shows that fatalities are higher among male patients (14 cases) compared to females (9 cases); however, the difference is not statistically significant (p=0.67). Similarly, no significant associations were observed between outcomes and residence (p=0.412), age (p=1.00),

or nutritional status (p=1.00). Overall, these findings suggest that baseline characteristics, including sex, age, domicile, and nutritional status, are not significantly linked to patient outcomes (Table 3).

Table 3. The relationship between baseline characteristics and clinical outcomes of APAKI patients

Variable	Outcome		OR	95% CI	p-value[a]
	Survived (n = 8)	Died (n = 23)			
Sex					
Male	6	14	0.52	0.085-3.156	0.67
Female	2	9			
Age					
1-5 Years	8	21	0.72	0.578-0.907	1.00
>5-18 Years	0	2			
Residence					
Outside Banda Aceh	6	12	0.36	0.062-2.194	0.412
Banda Aceh	2	11			
Nutritional status					
Good	7	18	1.94	0.192-19.741	1.00
Poor	1	5			

[a]All bivariate analyses were performed using Fisher's Exact Test due to expected cell counts <5 in the 2×2 contingency tables (small sample size, n=31). OR = odds ratio; 95% CI = 95% confidence interval.

Bivariate analysis shows that respiratory symptoms are significantly associated with clinical outcomes, with an OR 16 (95% CI: 1.643–155.77; p=0.01), indicating a 16-fold higher risk of death. A PELOD-2 score equal to or exceeding 10 is associated with a 10.89 times higher risk of mortality (OR=10.89; 95%CI: 1.140–103.98; p=0.03). Other variables, including fever, neurological, gastrointestinal, genitourinary symptoms, comorbidities, syrup medication history, and length of stay, showed no significant association (Table 4).

Tabel 4. Association Between Clinical Profile and Outcome in Children with APAKI

Variable	Outcome		OR	95% CI	p-valuea
	Survived (n=8)	Died (n=23)			
Fever					
Yes	7	18	0.51	0.051-5.221	1.00
No	1	5			
Neurological symptoms					
Yes	1	7	3.06	0.315-29.815	0.64
No	7	16			
Gastrointestinal symptoms	4	15	1.87	0.367-9.570	0.67
Yes	4	8			
No					
Respiratory symptoms					
Yes	1	16	16.00	1.643-155.77	0.01
No	7	7			
Genitourinary symptoms					
Yes	7	20	0.95	0.085-10.725	1.00
No	1	3			
Comorbidities					
Yes	1	3	1.05	0.093-11.824	1.00
No	7	20			
PELOD-2 Score					
≥10	1	14	10.89	1.140-103.98	0.03
<10	7	9			

Variable	Outcome		OR	95% CI	p-valuea
	Survived (n=8)	Died (n=23)			
History of syrup medication use					
Yes	6	15	0.62	0.102-3.841	1.000
No	2	8			
Length of stay					
≥ 3 days	8	15	0.652	0.484-0.879	0.076
< 3 days	0	8			

[a]All bivariate analyses were performed using Fisher's Exact Test due to expected cell counts <5 in the 2×2 contingency tables (small sample size, n=31). OR = odds ratio; 95% CI = 95% confidence interval.

Mechanical ventilator use was significantly associated with patient mortality (OR=16; 95% CI: 1.643–155.77; p=0.01), indicating a 16 times higher risk of death with ventilator use. Other therapies such as fomepizole (p=0.15), steroids (p=0.67), anticoagulants (p=1.00), and dialysis (p=0.40) did not show statistically significant associations with outcomes (Table 5).

Table 5. Association Between Therapeutic Profile and Outcome in Children with APAKI

Variable	Outcomes		OR	95% CI	p-value[a]
	Survived (n = 8)	Died (n = 23)			
Fomepizole					
Yes	2	1	0.13	0.100-1.772	0.15
No	6	22			
Steroids					
Yes	4	8	0.53	0.104-2.722	0.67
No	4	15			
Anticoagulants					
Yes	0	2	0.50	1.103-1.729	1.00
No	8	21			
Ventilator Use					
Yes	1	16	16.00	1.643-155.77	0.01
No	7	7			
Dialysis Therapy					
Yes	4	16	2.28	0.441-11.855	0.40
No	4	7			

[a]All bivariate analyses were performed using Fisher's Exact Test due to expected cell counts <5 in the 2×2 contingency tables (small sample size, n=31). OR = odds ratio; 95% CI = 95% confidence interval.

Abnormal leukocyte counts are strongly associated with higher mortality (OR=11.11; 95% CI: 1.701–72.564; p=0.01). Thrombocytopenia increases the risk of death nearly two-fold (OR=1.90; 95% CI: 1.207–2.957; p<0.001). Elevated urea (OR=13.2; 95% CI: 1.124-154.920; p=0.04), increases creatinine (OR=36.67; 95% CI: 3.124-430.333; p=0.02), reduces eGFR (OR=22; 95% CI: 1.924-251.539; p=0.01), and elevates liver enzymes, SGOT (OR=22; 95% CI: 1.924-251.539; p=0.01) and SGPT (OR=36.67; 95% CI: 3.124-430.333; p<0.001), are all significantly associated with poorer outcomes. Conversely, toxicology screening shows a protective effect, as patients who underwent testing has a markedly reduced risk of death (OR 0.07; 95% CI: 0.006–0.889; p=0.04) (Table 6).

Table 6. Association Between Laboratory Profile and Outcome in Children with APAKI

Variable	Outcomes		OR	95% CI	p-value[a]
	Survived (n = 8)	Died (n = 23)			
Hemoglobin					
Normal	3	2	6.30	0.821-48.342	0.09
Abnormal	5	21			
Leukocytes					
Normal	5	3	11.11	1.701-72.564	0.01
Increased	3	20			
Platelets					
Normal	8	9	1.90	1.207-2.957	0.00
Decreased	0	14			
NLR					
Normal	4	12	0.92	0.183-4.583	1
Abnormal	4	11			
Urea					
Normal	3	1	13.2	1.124-154.920	0.04
Increased	5	22			
Creatinine					
Normal	5	1	36.67	3.124-430.333	0.02
Increased	3	22			
eGFR					
Normal	4	1	22.00	1.924-251.539	0.01
Decreased	4	22			
SGOT					
Normal	4	1	22.00	1.924-251.539	0.01
Increased	4	22			
SGPT					
Normal	5	1	36.67	3.124-430.333	0.00
Increased	3	22			
CRP					
Normal	3	4	2.85	0.475-17.104	0.33
Abnormal	5	19			
PCT					
Normal	1	1	3.14	0.173-57.082	0.45
Abnormal	7	22			
Toxiology test					
Performed	3	1	0.07	0.006-0.889	0.04
Not Performed	5	22			

[a]All bivariate analyses were performed using Fisher's Exact Test due to expected cell counts <5 in the 2×2 contingency tables (small sample size, n=31). OR = odds ratio; 95% CI = 95% confidence interval.

DISCUSSION

This study provides clinical evidence that APAKI represents a severe multisystem toxic syndrome rather than an isolated renal disorder, with outcomes driven primarily by systemic involvement. This study was conducted on 31 pediatric cases of APAKI treated at Dr. Zainoel Abidin General Hospital in Banda Aceh between June and December 2022. The majority of patients in this study were male (64.5%) and aged between 1 and 5 years (93.5%). This demographic pattern reflects the population most affected during the 2022 outbreak of toxin-associated acute kidney injury in Indonesia, where previously healthy young children rapidly developed severe renal impairment. The predominance of males in this cohort aligns with findings reported by Bastani et al. and Hidayat et al., suggesting that sex-related differences may reflect exposure patterns or sociocultural factors rather than intrinsic biological susceptibility.[5,9] However, this observation contrasts with broader epidemiological data suggesting that female sex may be associated with increased susceptibility to acute kidney injury, as noted in the KDIGO

guidelines.[10] Experimental and clinical evidence, including studies by Silbiger et al., suggest that estrogen may exert renoprotective effects through anti-inflammatory, antioxidant, and vasodilatory mechanisms, potentially mitigating kidney injury.[11] This discrepancy indicates that sex-based differences in APAKI may be influenced more by exposure patterns, healthcare-seeking behavior, or sociocultural factors rather than intrinsic biological susceptibility alone.

The predominance of children aged 1–5 years in this study is also consistent with previous reports.[5,12] This age group is particularly vulnerable to toxic exposures due to several factors, including higher metabolic rates, immature detoxification systems, and behavioral tendencies that increase exposure risk. Importantly, syrup-based medications are widely used in this population due to ease of administration, palatability, and caregiver preference. In the present study, 67.74% of patients were reported to have consumed syrup medications before the onset of APAKI symptoms, reinforcing the strong epidemiological link between contaminated pharmaceutical products and disease occurrence. Similar patterns have been observed in global outbreaks of diethylene glycol (DEG) and ethylene glycol (EG) poisoning, where children are disproportionately affected due to liquid formulation exposure.[13] These findings highlight the critical importance of pharmaceutical safety regulations and post-market surveillance, particularly for pediatric formulations.

Most patients in this study has good nutritional status (80.6%), which is consistent with findings by Nadhif et al.[14] While malnutrition has been widely recognized as a risk factor for increased susceptibility to infections and adverse clinical outcomes, its role in acute toxic kidney injury appears to be less pronounced. Previous studies have demonstrated that malnutrition may exacerbate AKI progression through mechanisms such as impaired immune response, reduced antioxidant capacity, and altered drug metabolism.[15,16] However, in the context of APAKI, where the primary insult is acute toxic exposure rather than chronic physiological stress, nutritional status may play a less significant role in determining outcomes. This is supported by the absence of a statistically significant association between nutritional status and mortality in this study. It is plausible that the overwhelming toxic insult in APAKI may overshadow the modulatory effects of baseline nutritional condition, thereby reducing its prognostic relevance.

The mortality rate observed in this study is notably high, reaching 74.2%, exceeding rates reported by Nadhif et al. (57.7%).[14] This elevated mortality likely reflects a combination of factors, including delayed diagnosis, late presentation to healthcare facilities, and limited access to critical interventions such as dialysis and antidotal therapy.[17] In resource-limited settings, delays in recognizing toxin-induced AKI can result in missed opportunities for early intervention, including the administration of fomepizole or ethanol as antidotes and timely initiation of renal replacement therapy.[18] Furthermore, during the early phase of the outbreak, limited awareness among healthcare providers and the absence of clear clinical guidelines may have contributed to suboptimal management. These findings underscore the importance of rapid public health response, early warning systems, and clinician education in mitigating mortality during similar outbreaks.

Most patients in this study came from areas outside Banda Aceh, including districts such as Aceh Besar, Pidie Jaya, Bireun, North Aceh, Bener Meriah, Central Aceh, Langsa, Southwest Aceh, West Aceh, and South Aceh. This indicates a disparity in access to healthcare services, including limitations in early diagnosis and referral systems. Fever is the most frequently reported symptom (80.6%), which is consistent with reports by Bastani et al., O'Brien et al., and Hidayati et al., who all identified fever as the most common initial complaint.[5,9,19] The febrile response in DEG/EG intoxication can be explained by an inflammatory mechanism that triggers prostaglandin release, thereby increasing the hypothalamic set-point for body temperature regulation.[20]

The most commonly observed symptoms in this study were genitourinary manifestations, such as oliguria and anuria, found in 90.3% of patients. This finding is consistent with the studies by Hidayati et al., Bastani et al., and O'Brien et al., indicating that kidney failure is a principal clinical feature of APAKI.[5,9,19] The metabolism of DEG and EG produces calcium oxalate crystals, which irritate and damage renal tubules.[21]

Although genitourinary manifestations reflect the primary renal involvement in APAKI, our study found that these symptoms are not significantly associated with patient outcomes. This finding is consistent with the understanding that such manifestations are core diagnostic features of acute kidney injury, as defined by the KDIGO Acute Kidney Injury criteria, and therefore occur in the majority of affected patients regardless of disease severity.[10] Because oliguria/anuria is highly prevalent across cases, it demonstrates limited variability between survivors and non-survivors, reducing its utility as a prognostic discriminator. KDIGO itself emphasizes that urine output criteria are highly sensitive for AKI detection but are not independently sufficient for prognostication, which instead requires assessment of overall severity and systemic involvement. Moreover, APAKI should be understood as a multisystem disorder rather than an isolated renal condition. Toxic alcohol exposure leads to widespread metabolic disturbances, including severe metabolic acidosis, oxidative stress, and mitochondrial dysfunction, which affect multiple organ systems.[22] Mortality is therefore more closely related to the extent of systemic toxicity and multiorgan failure than to renal dysfunction alone. This is supported by the findings of this study, where respiratory symptoms, need for mechanical ventilation, and elevated PELOD-2 scores were significantly associated with poor outcomes. These variables reflect the severity of systemic illness and provide a more comprehensive assessment of patient prognosis. Moreover, due to this statistical phenomenon, our study found that the "seemingly protective" effect of oligouria/anuria is a contradiction and is primarily a statistical artifact rather than a true biological protective effect.

Respiratory, gastrointestinal, and neurological symptoms are also frequently observed. A total of 61.3% of patients experience gastrointestinal symptoms, in line with findings by Bastani et al., O'Brien et al., and Hidayati et al., which are attributed to mucosal irritation of the gastrointestinal tract by toxic metabolites.[5,9,19,23] Respiratory symptoms are present in 54.8% of patients and may be explained by systemic inflammatory effects due to AKI through cytokine-mediated pathways.[24,25] Neurological manifestations emerges in the later stages as a result of direct toxicity to the central and peripheral nervous systems.[5,21]

This study also demonstrates a significant association between PELOD-2 scores, respiratory symptoms, use of mechanical ventilation, and various laboratory parameters with patient outcomes. A PELOD-2 score of ≥10 was associated with higher mortality, consistent with the findings of Dewi et al., and supports the role of this score as a predictor of organ dysfunction.[26-28] Leukocytosis and thrombocytopenia are also significantly associated with mortality, as previously reported in studies highlighting active inflammatory processes and platelet dysfunction as important clinical indicators.[29–31]

Based on the results of this study, a significant association was found between urea and creatinine levels and the clinical outcomes of patients with APAKI. This finding is consistent with the study by Conroy et al., which reported that blood urea nitrogen (BUN) is a marker associated with the severity of AKI and may serve as a predictor of mortality.[32] Regarding creatinine, a study by Bagga et al. stated that even minor changes in serum creatinine (SCr) levels are linked to higher mortality.[33] Consequently, SCr is used in kidney injury classification systems for AKI to categorize the severity of the condition. This classification itself has been associated with longer hospital stays and a higher risk of mortality.[34]

A decrease in glomerular filtration rate (GFR) is observed in 83.8% of patients and is also associated with increased mortality, supporting its use in the pRIFLE system.[35] This study demonstrates an association between SGOT and SGPT levels and the clinical outcomes of patients with APAKI. Elevated liver enzymes (SGOT and SGPT) are also found, indicating the involvement of hepatorenal syndrome or renal-hepatic crosstalk,[36,37] as previously reported in APAKI patients. In addition, increased inflammatory markers such as CRP and PCT in deceases patients reinforce the role of systemic inflammation in disease progression.[5]

From a management perspective, diagnostic and therapeutic limitations played a critical role in patient outcomes. In this study, only 12.9% of patients underwent toxicology testing, largely due to early admission before WHO alerts. However, patients who received testing and timely diagnosis has better survival prospects.[5] Patients with timely diagnosis demonstrate

better survival, highlighting the importance of early toxicological confirmation. The use of fomepizole as an antidote was documented in only 9.6% of cases, significantly lower than in other studies, reflecting resource limitations and delayed response at the onset of the outbreak.[14]

The high proportion of patients requiring dialysis and mechanical ventilation reflects the severity of illness in this cohort. Both interventions are associated with poorer outcomes, consistent with previous studies, although this likely reflects underlying disease severity rather than treatment effects.[38,39] Prolonged hospital stay is also associated with worse prognosis, possibly due to complications such as secondary infections and prolonged organ dysfunction.

This study is interpreted in light of several limitations. First, it only included patients who were treated at Dr. Zainoel Abidin General Hospital, and therefore does not represent all APAKI cases in Aceh. Second, toxicological examinations were not performed on all patients, particularly those who were admitted before the WHO alert. Third, the lack of complete information regarding the types and sources of syrup medications consumed made it difficult to determine the etiology directly. Fourth, while statistical analysis shows significant prognostication correlation, due to the lack of multivariate analysis they cannot be firmly established as an independent predictor. The latter part also calls for another future research to conduct a multivariate analysis to reinforce the findings of current study.

Nevertheless, this study provides important insights into the clinical spectrum, laboratory profile, and prognostic factors of APAKI in children. The findings highlight the need for early diagnosis, public education, and the availability of toxicological testing and dialysis therapy. These findings may inform future outbreak preparedness strategies, particularly in resource-limited settings where early detection and access to antidotes remain challenging. The implications for SDG 3 (Good Health and Well-being) are evident, particularly in ensuring access to safe medications and strengthening pediatric healthcare systems. Enhancing the regulation of syrup-based medications and promoting equitable access to healthcare services in remote areas are also critical steps to prevent similar incidents in the future.

CONCLUSION

Based on the results of this study, the bulk of subjects are male, aged 1–5 years, residing in districts or cities outside Aceh Province, and had good nutritional status. The most common clinical manifestation of APAKI is genitourinary symptoms, while respiratory disorders are significantly associated with clinical outcomes. A PELOD-2 score of ≥10 is correlated with poor clinical outcomes. Most APAKI patients at Dr. Zainoel Abidin Hospital underwent dialysis therapy and mechanical ventilation, both of which are associated with patient outcomes. Laboratory parameters including leukocyte count, platelet count, urea, creatinine, eGFR, SGOT, SGPT, and toxicology results are also linked to patient outcomes. Future research should involve multicenter data across Indonesia focusing on syrup medication names and compositions, as well as further investigation of mortality risk factors in APAKI patients related to toxicology findings.

CONFLICT OF INTEREST

The authors state that they have no financial, commercial, or personal relationships that could be interpreted as potential conflicts of interest regarding the research, authorship, or publication of this article.

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DATA AVAILABILITY

The data underlying this study's findings can be obtained from the corresponding author upon reasonable request. However, the datasets are not openly accessible as they contain

sensitive patient information and are restricted by institutional ethical and confidentiality regulations.

SUPPLEMENTAL DATA

This study does not include any accompanying documents.

AUTHOR CONTRIBUTIONS

F designed the study, collected and analyzed the data, and drafted the manuscript. NS contributed to the study conception, supervised the research process, and provided critical revision of the manuscript. SH, SY, and HH contributed to patient data interpretation, clinical input, and manuscript review. JI provided methodological guidance, supervised data analysis, and approved the final version of the manuscript. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work.

DECLARATION OF USING AI IN THE WRITING PROCESS

The author used artificial intelligence (AI)-based technologies in a limited manner to assist with paraphrasing and academic language refinement in the English version of this manuscript. All scientific content and data interpretation remain entirely the author's original work.

LIST OF ABBREVIATIONS

AKI: Acute Kidney Injury; APAKI: Atypical Progressive Acute Kidney Injury; BPOM: Indonesian Food and Drug Authority; BUN: Blood Urea Nitrogen; DEG: Diethylene Glycol; EG: Ethylene Glycol; GFR: Glomerular Filtration Rate; MIS-C: Multisystem Inflammatory Syndrome in Children; ; RSUD: Regional General Hospital; SCr: serum creatinine.

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