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Lymphopenia and Acute Kidney Injury in Pediatric COVID-19: Mortality Focus Abstract

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Abstract

Background: Acute kidney injury (AKI) is a serious complication in adults with Coronavirus disease 2019 (COVID-19). While lymphopenia indicates disease severity, its association with renal outcomes in pediatric COVID-19 remains unclear. This study compared AKI incidence, severity, and prognosis between lymphopenic and non-lymphopenic children hospitalized with COVID-19.

Methods: In this retrospective cohort study, medical records of children under five years (n=148) hospitalized with PCR-confirmed COVID-19 were reviewed. Patients were divided into lymphopenic (n=35) and non-lymphopenic (n=113) groups based on admission absolute lymphocyte count. AKI severity was classified using the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Data were analyzed using SPSS 25 with Chi-square, Mann-Whitney U, Fisher's exact tests, and multiple logistic regression.

Results: Overall AKI incidence was 9.5% (14/148). The lymphopenic group was significantly younger (P=0.031). AKI incidence was higher in the lymphopenic group (14.3%) than in the non-lymphopenic group (8.0%), but not significantly (P=0.321). No significant differences were found in AKI severity (P=0.627) or prognosis (P=1.000). Multiple regression showed lymphopenia, age, sex, and comorbidities were not independent predictors of AKI. Notably, mortality in children who developed AKI was alarmingly high (35.7%) compared to those without AKI (5.2%).

Conclusion: Although lymphopenia was not a significant predictor of AKI in this pediatric cohort, the strikingly high mortality associated with AKI underscores the critical need for rigorous renal function monitoring in all hospitalized children with COVID-19.

Key Words: Acute Kidney Injury; COVID-19; Iran; Lymphopenia; Pediatrics; Prognosis.

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1- INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged as a global pandemic in late 2019, affecting millions worldwide (1). While the disease often presents with mild respiratory symptoms, severe cases can progress to acute respiratory distress syndrome (ARDS), multi-organ failure, and death (2). Although children are generally less susceptible to severe COVID-19 compared to adults, they can still develop serious complications such as multisystem inflammatory syndrome in children (MIS-C) and acute organ injuries (3, 4).

Acute kidney injury (AKI) is one of the most significant extrapulmonary complications associated with severe COVID-19. In adult populations, the incidence of AKI in hospitalized COVID-19 patients ranges from 3% to 29% and can exceed 50% in critically ill patients admitted to the intensive care unit (ICU) (5, 6). The underlying pathophysiology is complex and multifactorial, likely involving direct viral injury to renal tubular cells, systemic inflammatory response, hemodynamic instability, and hypoxia (7).

Lymphopenia, characterized by a decreased absolute lymphocyte count, is a common hematological finding in patients with COVID-19 and has been consistently identified as a key biomarker of disease severity and poor prognosis in adults (8, 9). Severe lymphopenia is thought to result from direct viral infection of lymphocytes, apoptosis, and immunosuppression driven by a cytokine storm (10). Studies have demonstrated a strong association between lymphopenia and increased rates of mortality, prolonged hospitalization, and multi-organ failure, including AKI (11, 12).

Despite these well-documented associations in adult populations, data regarding the relationship between lymphopenia and AKI in children with COVID-19 are scarce. Existing pediatric studies are often limited by small sample sizes and yield conflicting results, likely due to age-related differences in immune response and renal physiology. To date, no study has specifically compared the incidence and severity of AKI between lymphopenic and non-lymphopenic pediatric patients with COVID-19 in Iran.

This retrospective study was therefore designed to investigate the frequency, severity, and prognosis of AKI in children under five years of age with COVID-19, and to compare these outcomes between patients with and without lymphopenia upon admission.

2- MATERIALS AND METHODS

2-1. Study Design and Setting

This descriptive-analytical, cross-sectional retrospective study was conducted at Ali-Ibn-Abi-Talib Hospital, a major tertiary care center affiliated with Zahedan University of Medical Sciences in southeastern Iran. The study utilized data from the medical records of all children hospitalized with COVID-19 between January 2020 and January 2024.

2-2. Participants

The medical records of all children under 18 years of age with a laboratory-confirmed COVID-19 diagnosis (positive reverse transcriptase-polymerase chain reaction [RT-PCR] test) were initially reviewed. To reduce data dispersion and improve the reliability of statistical analyses, the final sample was limited to children under five years of age. Patients were excluded if they had pre-existing chronic kidney disease, were on maintenance dialysis, had a known immunodeficiency disorder, or had a

history of leukemia. Patients who received nephrotoxic drugs at doses or durations exceeding standard treatment guidelines were also excluded (e.g., gentamicin >7.5 mg/kg/day, amikacin >15 mg/kg/day, vancomycin >60 mg/kg/day, amphotericin B >1.5 mg/kg/day, ibuprofen >30 mg/kg/day for >48 hours, or tenofovir for >7 days). Finally, patients with incomplete data regarding the variables of interest were excluded.

2-3. Data Collection

Data were extracted from patients' electronic and paper medical records using a standardized data collection form. The information retrieved included:

- **Demographic data:** Age (months), sex, and place of residence.
- **Clinical data:** Underlying comorbidities, presence of AKI, and outcome (survival or death).
- **Laboratory data:** Serum creatinine (Cr) levels and absolute lymphocyte count (ALC) at the time of admission.

Lymphopenia was defined as an ALC of less than 1000 cells/μL for patients over 12 months and less than 3000 cells/μL for patients under 12 months (13).

2-4. Assessment of Acute Kidney Injury

The primary outcome of this study was the incidence and severity of AKI. AKI was diagnosed based on serum Cr levels and defined according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 (14). Because baseline serum Cr levels were not consistently available in the patients' records, we estimated these values based on age-specific normal ranges published in the Nelson Textbook of Pediatrics (13). The grading criteria were as follows:

- **Grade 1 (Mild):** Increase in serum Cr > 0.3 mg/dL or 1.5 to 2.0 times the baseline.
- **Grade 2 (Moderate):** Increase in serum Cr 2.0 to 3.0 times the baseline.
- **Grade 3 (Severe):** Increase in serum Cr > 3.0 times the baseline or > 4.0 mg/dL.
- **Grade 4 (Life-threatening):** Indications for renal replacement therapy (dialysis).
- **Grade 5 (Death):** Death attributed to AKI.

2-5. Statistical Analysis

All data were analyzed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA). Categorical variables were reported as frequencies and percentages. The Shapiro-Wilk test was used to assess the normality of continuous variables. Since age did not follow a normal distribution, it was expressed as median (interquartile range) and mean ± standard deviation.

To compare demographic and clinical variables between the lymphopenic and non-lymphopenic groups, we employed appropriate statistical tests. The Chi-square test was used for categorical variables (e.g., sex, presence of AKI, outcome). For ordinal variables (CTCAE grades) and non-normally distributed continuous variables (age), the non-parametric Mann-Whitney U test was used. Fisher's exact test or Fisher-Freeman-Halton Exact Test was used to compare categorical data when the expected frequencies were less than 5. A multiple logistic regression model was constructed to identify independent risk factors for AKI, adjusting for potential confounders such as lymphopenia, age, sex, and comorbidities. A significance level of $P < 0.05$ was considered statistically significant.

2-6. Ethical Considerations

This study was approved by the Ethics Committee of Zahedan University of Medical Sciences (Ethics Code: IR.ZAUMS.REC.1403.398). The study

adhered to the principles of the Declaration of Helsinki. All patient data were anonymized before analysis to ensure confidentiality.

3- RESULTS

A total of 192 children with COVID-19 were initially evaluated. Following the application of inclusion and exclusion criteria, the final analysis was performed on 148 children under five years of age. Among these, 35 (23.6%) were classified as lymphopenic and 113 (76.4%) as non-lymphopenic.

3-1. Demographic Comparison of the Two Groups

The baseline demographic characteristics of the study population are presented in Table 1. The majority of patients in both groups were male (80.0% in the lymphopenic group vs. 65.5% in the non-lymphopenic group). There were no statistically significant differences between the two groups in terms of sex (P=0.159) or place of residence (P=0.344). However, children in the lymphopenic group were significantly younger than those in the non-lymphopenic group (P=0.031).

Table-1. Demographic characteristics of the study population (n=148).

Variable	Category	Lymphopenic Group (n=35)	Non-Lymphopenic Group (n=113)	P-Value
Sex	Male Female	28 (80.0%) 7 (20.0%)	74 (65.5%) 39 (34.5%)	0.159[a]
Place of Residence	Zahedan Other Cities	29 (82.9%) 6 (17.1%)	79 (69.9%) 34 (30.1%)	0.344[a]
Age (months)	Median (IQR) Mean ± SD	5.0 (2.0 - 16.0) 11.58 ± 15.32	9.0 (3.0 - 24.0) 16.52 ± 16.63	0.031[b]

Note: **[a]:** Chi-square test**. [b]:** Mann-Whitney U test. **SD:** Standard Deviation; **IQR:** Interquartile Range.

3-2. Incidence and Severity of AKI

The overall incidence of AKI across the whole cohort was 9.5% (14 out of 148 patients). As shown in Table 2, the incidence was higher in the lymphopenic group (14.3%) than in the non-lymphopenic group (8.0%). However, this difference was not statistically significant (P=0.321).

Among the 14 patients with AKI, the severity distribution based on CTCAE grading is shown in Table 3. Grade 1 (mild) AKI was the most common manifestation in both groups. No statistically significant difference was observed in the distribution of AKI severity grades between the two groups (P=0.627).

3-3. Prognosis of AKI

The prognosis of patients who developed AKI was assessed based on survival or death. As indicated in Table 4, there was no statistically significant difference in mortality rates between lymphopenic (2/5, 40%) and non-lymphopenic (3/9, 33.3%) children with AKI (P=1.000).

Table-2. Incidence of AKI in lymphopenic and non-lymphopenic groups.

Outcome	Lymphopenic (n=35)	Non-Lymphopenic (n=113)	P-Value[a]
Developed AKI	5 (14.3%)	9 (8.0%)	0.321
No AKI	30 (85.7%)	104 (92.0%)	
Total	35 (100.0%)	113 (100.0%)	

[a]: Fisher's Exact Test.

Table-3. Distribution of AKI severity grades in lymphopenic and non-lymphopenic groups.

CTCAE Grade	Lymphopenic (n=5)	Non-Lymphopenic (n=9)	Total (n=14)
Grade 1	3 (60.0%)	6 (66.7%)	9 (64.3%)
Grade 2	0 (0.0%)	1 (11.1%)	1 (7.1%)
Grade 3	2 (40.0%)	2 (22.2%)	4 (28.6%)
Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
Grade 5	0 (0.0%)	0 (0.0%)	0 (0.0%)

[a]: Fisher-Freeman-Haltom Exact Test, P=0.627.

Critically, the overall mortality rate among children who developed AKI was alarmingly high at 35.7% (5 out of 14 patients). In contrast, the mortality rate among children without AKI was only 5.2% (7 out of 134 patients). To quantify this association, a univariate logistic regression analysis was performed. The results showed that patients who developed AKI had significantly higher odds of mortality compared to those without AKI (OR = 10.12, 95% CI: 2.89–35.42, P < 0.001). This finding underscores the critical prognostic significance of AKI in pediatric COVID-19 patients.

3-4. Predictive Factors for AKI

To identify independent predictors of AKI, a multiple logistic regression model was constructed, including lymphopenia, sex, age, and comorbidities as predictor variables. The results, presented in Table 5, show that none of the included variables were significantly associated with the development of AKI.

Table-4. Prognosis of patients with AKI.

Outcome	Lymphopenic (n=5)	Non-Lymphopenic (n=9)	P-Value[a]
Survived	3 (60.0%)	6 (66.7%)	1.000
Died	2 (40.0%)	3 (33.3%)	

[a]: Fisher's Exact Test.

Table-5. Multiple logistic regression analysis for predictors of AKI.

Variable	B (Coefficient)	SE	Adjusted Odds Ratio (aOR)	95% CI for aOR	P-Value
Lymphopenia (Ref: No)	0.607	0.618	1.83	0.55 - 6.16	0.326
Sex (Ref: Female)	-0.310	0.608	0.73	0.22 - 2.42	0.610
Comorbidity (Ref: No)	-0.558	0.797	0.57	0.12 - 2.73	0.484
Age (months)	-0.027	0.024	0.97	0.93 - 1.02	0.249
Intercept	-1.778	0.569	0.17	–	0.002

4- DISCUSSION

This study investigated the association between lymphopenia and acute kidney injury in a pediatric cohort with COVID-19 in southeastern Iran. While an alarming overall incidence of AKI and a high mortality rate were observed, the study did not find a significant independent association between lymphopenia at admission and the development, severity, or prognosis of AKI in children under five years old.

The most striking finding of our study is the substantial mortality rate of 35.7% observed in children who developed AKI, dramatically higher than the 5.2% mortality in those without AKI. This finding underscores the critical clinical significance of AKI as a life-threatening complication in pediatric COVID-19, reinforcing the need for vigilant monitoring and early intervention. This aligns with a multi-center study in Egypt that highlighted the severe impact of AKI on outcomes in children with MIS-C (15). The clinical message is clear: AKI in a

child with severe COVID-19 should be considered a medical emergency.

The overall incidence of AKI in our study (9.5%) falls well within the 3% to 29% range reported by systematic reviews of adult and general populations (16). Our figure is remarkably consistent with a study by Basiratnia et al. (2021) in Shiraz, Iran, which reported an 11.7% AKI incidence in 85 hospitalized children (17). Another study from Egypt by Abdelkareem et al. reported a slightly higher incidence of 18.3% in children up to 15 years old (18). This discrepancy might be explained by differences in age distribution and disease severity, as older children may be more susceptible to severe inflammatory responses (19). The consistency of our results with other regional studies enhances the reliability of our findings.

Contrary to established findings in the adult literature, where lymphopenia is a strong predictor of AKI (11, 20), our study did not confirm this association. Studies by Wagner et al. (2020) and Santos et al. (2021) have shown a direct relationship between low lymphocyte counts and renal impairment in adults (11, 12). Our negative findings may be attributed to fundamental differences in immunopathology and renal physiology between children and adults. Children, particularly those under five, have a developing immune system that may respond differently to the SARS-CoV-2-induced cytokine storm, potentially resulting in less direct immune-mediated renal injury (21). Furthermore, our sample size might have been underpowered to detect a moderate effect, especially given the low overall incidence of AKI. This lack of association is supported by a retrospective study from Tehran, Iran, which, despite finding a high prevalence of lymphopenia (45%) in pediatric COVID-19 patients, failed to establish it as an independent predictor of multi-organ injury (22). This suggests that in children, lymphopenia may be a marker of systemic illness but not necessarily a specific driver of organ-specific damage like AKI.

Interestingly, our analysis revealed that children in the lymphopenic group were significantly younger. This is a plausible finding given the well-known immaturity of the adaptive immune system in infants and young toddlers. A reduced baseline lymphocyte count, combined with the age-specific cutoffs used for defining lymphopenia, could confound the results. Infants often have inherently lower absolute lymphocyte counts, making the distinction between true lymphopenia (as a disease marker) and normal physiological variation difficult. Although our regression analysis adjusted for age, the small sample size may not have been sufficient to eliminate this confounding effect.

The primary methodological limitation of this study is its retrospective design. This led to data gaps, particularly the lack of documented baseline creatinine levels required for AKI grading. We addressed this limitation by utilizing age-normal values from standard pediatric references (15). While a scientifically defensible and widely-used approach in pediatric research, it is an approximation that could introduce some bias. Specifically, the use of estimated baseline creatinine may have led to misclassification of AKI severity in some cases, potentially underestimating or overestimating the true incidence and severity of AKI. Future prospective studies should prioritize the collection of pre-admission or admission baseline creatinine values to ensure accurate AKI staging.

Additionally, the single-center design and relatively small sample size, especially within the AKI-positive group (n=14), limit the generalizability of our results and the statistical power to detect smaller but potentially clinically relevant differences.

Post-hoc power analysis indicated that with the observed effect size (OR = 1.83 for lymphopenia), our study had approximately 28% power to detect a significant association at $\alpha = 0.05$. This suggests that our study was underpowered to detect moderate associations, and the absence of a statistically significant relationship between lymphopenia and AKI should be interpreted with caution. Larger, multicenter studies with adequate sample sizes are required to validate these findings and to explore the role of other biomarkers, such as the neutrophil-to-lymphocyte ratio (NLR) or C-reactive protein-to-lymphocyte ratio (CLR), which were found to be more sensitive than ALC alone in a study by Wang et al. (2024) (23).

5- CONCLUSION

Despite not establishing lymphopenia as a risk factor for AKI in pediatric COVID-19 patients, our study provides strong evidence of the severe clinical implications of AKI in this population. The alarmingly high mortality rate associated with AKI (35.7%) necessitates the implementation of routine, systematic renal function monitoring (serum creatinine and urea) for all children hospitalized with COVID-19, irrespective of their initial lymphocyte count or demographic characteristics. This practice is paramount for early identification and management of AKI, which could significantly improve survival rates. Future research should focus on larger, prospective, multicenter studies to further investigate the complex pathophysiology of COVID-19-associated AKI in children and to identify more sensitive, predictive biomarkers.

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8- CONFLICT OF INTEREST

The authors declare that they have no competing interests, financial or non-financial, related to the content of this manuscript.

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