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Predictors of mortality in critically ill children hospitalized with laboratory- confirmed COVID-19 pneumonia

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Abstract

Background Children with COVID-19 infection had fewer severe symptoms, which made it challenging to publish clinical data for this age group. This study aimed to determine the clinical features, laboratory markers, and predictors of mortality in children hospitalized in Pediatric Critical Care Units with COVID-19 pneumonia.

Methods This retrospective research included all children between the age of ≥ 1 month and 18 years with laboratory-confirmed COVID-19 pneumonia through reverse transcriptase polymerase chain reaction (RT-PCR) from nasopharyngeal swabs who were admitted to Pediatric Critical Care Units between January 2022 and December 2022.

Results The study included 62 patients with confirmed COVID-19 infection. Out of the 62 patients, 43 (69.4%) survived and 19 (30.6%) succumbed. High-grade fever, cough, altered level of consciousness, convulsion, CO-RADS IV, elevated blood CRP, urea, D-dimer, ferritin, and sodium were linked to significantly higher mortality risk. (OR: 15.867, $p=0.001$, OR: 1.543, $p=0.044$, OR: 7.321, $p=0.026$, OR: 15.00, $p=0.017$, OR: 10.833, $p=0.001$, OR: 1.015, $p=0.032$, OR: 1.028, $p=0.040$, OR: 3.315, $p<0.0001$, OR: 1.004, $p=0.049$, OR: 1.111, $p=0.006$ respectively).

Conclusion Our study revealed high in-hospital mortality among critically ill children with confirmed COVID-19 pneumonia. Identification of critically ill children with risk factors for death, such as high-grade fever, cough, altered consciousness, convulsion, CO-RADS IV and V, and raised inflammatory markers at the time of admission could minimize excess mortality during COVID-19 waves.

Keywords Children, COVID-19, Critical, Mortality, Predictors

Background

According to World Health Organization (WHO) data, the COVID-19 pandemic has led to a high overall mortality rate, with concerning trends showing an increasing mortality among those under the age of 20 [1].

International pediatric statistics show reduced prevalence of severe COVID-19 infection in children and higher rates of asymptomatic infection [2]. Few children with COVID-19 require hospitalization, especially those under one year of age, and even fewer require PICU admission [3]. Pediatric COVID-19 cases represented less than 8% of all confirmed cases, according to national research, and the percentage of cases with severe or critical illness varied from 3.3% to 8% [4].

During the several waves of the pandemic, the reported illness burden and mortality rates varied significantly by age group. COVID-19 in children is known to normally cause mild-to-moderate disease [5]. Additionally, some studies claim that infants under 1 year olds are the age group with the highest mortality rates, even if it appears

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that fewer children are developing catastrophic sequelae such multisystem inflammatory syndrome (MIS-C) [6].

Positive RT-PCR results from a nasopharyngeal swab remain the gold standard for laboratory diagnosis of COVID-19. However, additional testing that includes deep bronchial and fecal samples is occasionally advised due to the possibility of false negative results [7].

In this study, we aimed to identify predictors of mortality in critically ill children with COVID-19 pneumonia.

Materials and methods

This retrospective research included all children between the age of ≥ 1 month and 18 years with laboratory-confirmed COVID-19 pneumonia through reverse transcriptase polymerase chain reaction (RT-PCR) who admitted to Pediatric Intermediate and Intensive Care Units at Minia Health Insurance Hospitals and Minia University Hospital of Pediatrics in Egypt between January 2022 and December 2022.

Data collection

Demographic and clinical data such as age, sex, clinical manifestations, pre-existing comorbidities, severity of COVID-19 pneumonia at admission which was assessed using respiratory index of severity scoring system for HIV non-infected children (RISC) [8], type of admission, presence of multisystem inflammatory syndrome in children (MIS-C), and laboratory results at admission, such as complete blood count (CBC), D-Dimer, Ferritin, C-reactive protein (CRP), Lactate dehydrogenase (LDH), blood urea, serum creatinine, Aspartate transaminase (AST), Alanine transaminase (ALT), serum electrolytes (Na, K, ionized Ca), and chest x-ray, and chest computed tomography (CT) scan results, were reviewed, and recorded from the electronic medical records of the patients.

Approval for this study was granted by the Institutional Review Board and Medical Ethics Committee, Faculty of Medicine, Al-Azhar University ID (MSR/AZ.AST. / PED025/23/218/4/2023). This study was performed in line with the principles of the Declaration of Helsinki and its later amendments. Written informed consent from the patients' guardians could not be obtained due to the retrospective nature of the study.

Statistical analysis

Data were collected in a spreadsheet using Microsoft Excel 2013. The statistical software for social science (SPSS) version 23 was then used for statistical analysis. Quantitative data with a normal distribution were shown as mean and standard deviation, whereas categorical data were shown as numbers and percentages. Qualitative variables were compared using $\chi 2$ and Fisher exact tests. Mann–Whitney test was used to compare nonparametric quantitative variables. Binary logistic regression analysis was performed to estimate the risk factors for the disease mortality when $P < 0.05$. Receiver operating characteristics (ROC) curve was analyzed to assess the predictors of COVID-19 infection mortality. Statistical significance was considered $P < 0.05$.

Results

Patient characteristics

Sixty-two patients diagnosed with laboratory-confirmed COVID-19 infection using RT-PCR test were included in the study. Out of 62 patients, 43 (69.4%) were discharged, whereas 19 (30.6%) were succumbed. The median age of the deceased patients was lower than that of the survivors (18 vs. 24 months); they also experienced significantly higher grade fever ($p < 0.001$), cough ($p = 0.004$), disturbed consciousness ($p = 0.013$), and convulsion ($p = 0.003$) (Table 1).

A comorbid condition was present in 16.3% of the survivors, compared to 31.6% of the deceased patients who had at least one chronic medical condition. Asthma ($n = 3$) and congenital heart disease ($n = 4$) were the associated comorbid diseases in the survivors patients, while congenital biliary atresia ($n = 1$), congenital heart disease ($n = 1$), cerebral palsy ($n = 1$), diabetes mellitus ($n = 1$), and chronic kidney disease ($n = 2$) were all significantly more prevalent in the deceased cohort ($p = 0.017$).

The results of the chest CT scan which was performed within 48 h of patients' admission to the critical care units showed a highly significant difference between the survivors and non-survivors cohorts using the coronavirus reporting and data system (CO-RADS) ($p < 0.001$).

Laboratory findings

Hemoglobin level, platelet count, and serum ionized calcium level were all considerably lower in the deceased patients, while total leucocytic count, CRP, blood urea, serum creatinine, ALT, D-dimer, ferritin, LDH, and sodium levels were all significantly higher. The clinical characteristics and laboratory results of the patients who died and those who survived are illustrated in (Table 2).

The presence of high-grade fever, cough, altered consciousness, and/or convulsions was linked to a higher risk of mortality (OR: 15.867, $p = 0.001$, OR: 1.543, $p = 0.044$, OR: 7.321, $p = 0.026$, and OR: 15.00, $p = 0.017$, respectively) using a univariate binary logistic regression model. Also, elevated laboratory markers, including CRP, blood urea, D-dimer, serum ferritin, and sodium, were all strongly associated with an increased risk of mortality (OR: 1.015, $p = 0.032$, OR: 1.028, $p = 0.040$, OR: 3.315, $p < 0.001$, OR: 1.004, $p = 0.049$, OR: 1.111, $p = 0.006$ respectively) (Table 3).

Table 1 Demographic characteristics and clinical manifestations of the patients

Variables	Survived ($n=43$)	Deceased ($n=19$)	*P* value
Age (m) Median (IQR)	24.0 (6.0–72.0)	18.0 (4.0–120.0)	0.909
Age groups			
■ < 1 yr	14 (32.6%)	9 (47.4%)	0.183
■ 1-5yrs	16 (37.2%)	2 (10.5%)	
■ 5–10 yrs	8 (18.6%)	4 (21.1%)	
■ > 10yrs	5 (11.6%)	4 (21.1%)	
Sex			
■ Male	27 (62.8%)	11 (57.9%)	0.715
■ Female	16 (37.2%)	8 (42.1%)	
Weight Z score	0.027 ± 1.03	-0.06 ± 0.93	0.753
High grade fever	38.28 ± 0.69	39.11 ± 0.49	< 0.001*
Dyspnea	36 (83.7%)	19 (100.0%)	0.062
Cough	35 (81.4%)	19 (100.0%)	0.044*
Vomiting	9 (20.9%)	6 (31.6%)	0.367
Diarrhea	7 (16.3%)	1 (5.3%)	0.233
Disturbed conscious	2 (4.7%)	5 (26.3%)	0.013*
Convulsion	1 (2.3%)	5 (26.3%)	0.003*
O2 saturation%	39.33 ± 2.93	82.58 ± 11.42	< 0.001*
RISC			
■ 0	10 (23.3%)	0 (0.0%)	< 0.001*
■ 1	1 (2.3%)	0 (0.0%)	
■ 2	23 (35.5%)	2 (10.5%)	
■ 3	3 (7.0%)	3 (15.8%)	
■ 4	0 (0.0%)	1 (5.3%)	
■ 5	3 (7.0%)	3 (15.8%)	
■ 6	3 (7.0%)	10 (52.6%)	
CO-RADS of CT Chest			
■ I	5 (11.6%)	0 (0.0%)	< 0.001*
■ II	12 (27.9%)	0 (0.0%)	
■ III	22 (51.2%)	4 (21.1%)	
■ IV	4 (9.3%)	10 (52.6%)	
■ V	0 (0.0%)	5 (26.3%)	
Type of admission			
■ Intermediate Care Unit	34 (79.1%)	1 (5.3%)	< 0.001*
■ PICU	9 (20.9%)	18 (94.7%)	
Diagnosis of MIS-C	5 (11.6%)	1 (5.3%)	0.422
Need for MV	1 (2.3%)	18 (94.7%)	< 0.001*
Co-infection	16 (37.2%)	13 (68.4%)	0.03*

RISC Respiratory index of severity in children, *CO-RADS* COVID-19 Reporting and Data System, *PICU* Pediatric intensive care unit, *MIS-C* Multisystem inflammatory syndrome in children, *MV* Mechanical ventilation

*$P < 0.05$ is significant

Regarding CT Chest results, CO-RADS IV was significantly associated with a high risk of mortality (OR: 10.833, $p=0.001$). In addition, all children with CO-RADS V were deceased and this indicates both CO-RADS IV and V carried increased risk for mortality.

Using ROC curve analysis, D-dimer had the highest AUC, with serum creatinine coming in second. AUC for D-Dimer was 0.844 with a cut-off value of 1.7 (sensitivity = 84.2% and specificity = 84.1%). While blood creatinine was found to have a fair predictive ability for mortality with an AUC of 0.799 and a cut-off value of 0.9 (sensitivity = 63.2% and specificity = 88.4%), D-dimer was considered to have a strong mortality predictive power. (Table 4) provides the corresponding sensitivity and specificities of all laboratory parameters under the optimum cut-off values.

Discussion

Our findings revealed several variables linked to mortality in children with COVID-19 pneumonia. The likelihood that children may die from COVID-19 increases as they get younger. This outcome is consistent with a prior study, which found that children under the age of one had a more substantial proportion of severe and critical cases reaching 10.6% [9].

The mortality rate in our study was 30.6%. The majority of the patients who died were considerably younger than those who survived. This outcome was consistent with the findings of Dewi et al. [10], who found that 20 children (40%) of the 490 pediatric COVID-19 confirmed cases died. However, in their study, patients older than 10 years had the highest mortality rate.

Even though our findings and those of the earlier studies were in agreement, our study revealed a higher mortality rate because it was conducted during the fourth wave of COVID-19 infection (dominant omicron variant). The existence of co-infections, associated medical conditions, and the restricted healthcare resources in these institutions may all contribute to this high occurrence.

Nevertheless, Efendi et al. [11], reported that 62 (2.9%) of 2231 confirmed COVID-19 children died, with the chance of death decreasing by 0.94 times as the child's age advances.

The deceased patients in our group had significantly higher rates of fever, cough, disturbed consciousness, and convulsion. According to Parcha et al. [12], hospitalized children with severe illnesses had a higher prevalence of symptoms such as fever, and respiratory and gastrointestinal manifestations. Based on this result, it is important to assess symptoms in children with COVID-19 to determine indications for hospitalization to increase survival probability.

In the current research, comorbidities were present in 31.6% of the deceased patients. Chronic kidney disease was the most prevalent comorbidity (10.5%), followed by congenital biliary atresia, congenital heart disease, cerebral palsy, and diabetes mellitus.

Table 2 Laboratory characteristics of COVID-19 infected children

Variables	Survived ($n=43$) Median (IQR)	Deceased ($n=19$) Median (IQR)	*P* value
Hb (g/dL)	12.0 (10.7–13.0)	8.8 (8.0–10.0)	< 0.001*
TLC (10^9 /L)	10.0 (7.0—12.0)	12.0 (9.7.0—22.0)	0.044*
Leukocytosis > 11×10^9/L	13 (30.2%)	11 (57.9%)	0.039*
PLT (10^9 /L)	249.0 (200.0—308.0)	117.0 (90.0–180.0)	< 0.001*
Lymphocytes (10^9 /L)	2400.0 (1100.0–4500.0)	2310.0 (1410.0- 2800.0)	0.577
Neutrophils (10^9 /L)	4950.0 (3900.0–9709.6)	6050.0 (4200.0–9800.0)	0.630
N/L ratio	2.50 (1.92–5.00)	2.56 (1.67- 4.90)	0.945
CRP (mg/l)	13.0 (9.0- 48.0)	48.0 (12.0- 96.0)	0.021*
Urea (mg/dl)	27.0 (20.0- 34.0)	40.0 (30.0–50.0)	< 0.001*
Creatinine (mg/dl)	0.6 (0.5- 0.7)	1.0 (0.7- 1.5)	< 0.001*
AST (u/l)	30.0 (22.0- 35.0)	38.0 (24.0–55.0)	0.089
ALT (u/l)	28.0 (20.0- 37.0)	35.0 (29.0–50.0)	0.023*
D-dimer (ug/ml)	0.9 (0.6- 1.5)	3.0 (2.0- 4.0)	< 0.001*
Ferritin (ng/ml)	150.0 (127.0- 200.0)	220.0 (200.0–350.0)	< 0.001*
LDH (IU/L)	200.0 (155.0- 321.0)	300.0 (200.0–450.0)	0.041*
Na (mEq/L)	139.0 (136.0- 147.0)	150.0 (145.0–155.0)	0.005*
K (mEq/L)	4.0 (3.6- 4.5)	3.5 (2.7–5.0)	0.102
Ionized Ca (mmol/L)			

Normal laboratory reference values: Hb: 11- 14 gm/dl, TLC: 4–11×10^9/L, Platelet: 150–450×10^9/L, CRP: 0–0.5 mg/l, D-dimer: 0–0.5 ug/ml, ferritin: 30–150 ng/mL, LDH: 125–220 U/L, Na: 135–145 mEq/L, K: 3.5–5.5 mEq/L, Ionized Ca:1.2–1.3 mmol/l

Hb Hemoglobin, *TLC* Total leucocytic count, *PLT* Platelet, *N/L ratio* Neutrophil/ lymphocytic ratio, *CRP* C-reactive protein, *LDH* Lactate dehydrogenase, *AST* Aspartate transaminase, *ALT* Alanine transaminase, *Na* Sodium, *K* Potassium, *Ca* Calcium

**P* < 0.05 is significant

Table 3 Logistic regression analysis for the predictors of in-hospital mortality in children with COVID-19 pneumonia

Variable	Univariate analysis	
	OR (CI 95%)	*P* value
Fever	15.867 (3.224–78.097)	0.001
Cough	1.543 (1.268–1.878)	0.044
Disturbed consciousness	7.321 (1.274–42.067)	0.026
Convulsion	15.00 (1.612–139.583)	0.017
CO-RADS IV	10.833 (2.760–42.523)	0.001
Hb (g/dL)	0.352 (0.211–0.586)	< 0.001
CRP (mg/l)	1.015 (1.001–1.029)	0.032
Urea (mg/dl)	1.028 (1.001–1.056)	0.040
D-dimer (ug/ml)	3.315 (1.808–6.078)	< 0.001
Ferritin (microgram/L)	1.004 (1.000–1.008)	0.049
Na (mEq/L)	1.111 (1.031–1.198)	0.006

OR Odds ratio, *p* value < 0.05 is significant

CO-RADS COVID-19 Reporting and Data System, *Hb* Hemoglobin, *CRP* C-reactive protein, *Na* Sodium

This outcome is consistent with the findings of Solórzano-Santos et al. [13], who noted that chronic renal disease had the highest case fatality rate (4.30%) among the comorbidities. On the other hand, Kompaniyets et al. [14], found that children with type 1 diabetes, followed by congenital cardiovascular defects, epilepsy, obesity, and essential hypertension had a higher risk of severe illness while hospitalized.

Hematological abnormalities, such as reduced hemoglobin, lower platelet count, and higher leukocytic count, were more pronounced in the deceased group in our sample. This could be explained by diffuse alveolar damage that occurred in COVID-19 infection leads to decreased platelet count due to entrapped megakaryocytes in the injured lung and decreased its production by bone marrow from severe infection [15].

Elevated inflammatory markers have been linked to severe disease in children, according to research by Kainth et al. [16], and Zachariah et al. [17], which is consistent with our findings. However, Liguoro et al. [18], and Al Yazidi et al. [19], reported that elevated inflammatory markers were not commonly observed in children with COVID-19.

In our study, D-dimer (AUC = 0.844) and LDH (AUC = 0.723) exhibited very good and good accuracy in predicting mortality in patients with COVID-19, which is consistent with the findings of Keski [20]. Additionally, Huang et al. [21], reported in their

Table 4 ROC curve analysis of laboratory parameters for the prediction of mortality

Variables	Cut off	AUC	P value	95% CI	Sensitivity%	Specificity%
TLC	11,950	0.661	0.045	0.511- 0.811	52.6	74.4
CRP	46.5	0.684	0.022	0.530- 0.838	68.4	69.8
Urea	35.5	0.797	< 0.001	0.677- 0.918	63.2	86.0
Creatinine	0.9	0.799	< 0.001	0.664- 0.934	63.2	88.4
ALT	24	0.682	0.023	0.544- 0.819	100	27.9
D-dimer	1.7	0.844	< 0.001	0.729- 0.959	84.2	81.4
Ferritin	194	0.790	< 0.001	0.667- 0.914	84.2	69.8
LDH	195	0.723	0.005	0.574- 0.871	89.5	41.9
Na	143.5	0.664	0.041	0.520- 0.808	78.9	62.8

P value < 0.05 is significant, *TLC* Total leucocytic count, *CRP* C-reactive protein, *ALT* Alanine transaminase, *LDH* Lactate dehydrogenase, *Na* Sodium

meta-analysis that higher blood levels of D-dimer was related to higher mortality.

Keski [20], observed that using ferritin and CRP levels to predict death had very good accuracy, whereas our group showed a good and fair accuracy of ferritin and CRP levels, respectively.

There is a discussion surrounding the optimum cut-off values of these biomarkers, particularly in children. We, therefore, advise utilizing more prognostic models to evaluate these biomarkers with other established biomarkers of poor COVID-19 outcomes.

This study had some limitations. Firstly, due to the retrospective nature of this research, it's possible that some crucial details were missed due to inadequate documentation. Additionally, the sample size was small.

Conclusion

During COVID-19 waves, excess mortality may be reduced by identifying critically ill children who have risk factors for death at the time of admission, such as high-grade fever, cough, altered consciousness, convulsion, CO-RADS IV and V, and raised inflammatory markers. Children less than one year and those with associated medical diseases were more vulnerable to high death rates.

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Authors' contributions
All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Rehab Elmeazawy. The Manuscript was revised and edited by Ahmed Mohammed Farid EL-Moazen. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Institutional Review Board and Medical Ethics Committee, Faculty of Medicine, Al-Azhar University (Assiut) (MSR/AZ.AST./PED025/23/218/4/2023).
Written informed consent was obtained from all subjects of the study or their parents or guardians.

Consent for publication
Not Applicable.

Competing interests
The author (s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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